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Considerations for the Real-World Management of ARIA From the Aducanumab Phase 3 Studies EMERGE and ENGAGE

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OBJECTIVE

- To describe the characteristics of ARIA that occurred in participants treated with high-dose (10 mg/kg) aducanumab in EMERGE and ENGAGE in order to inform effective ARIA monitoring and management in real-world clinical practice.

CONCLUSIONS

- ARIA were mostly asymptomatic: 76% of aducanumab-treated participants with ARIA showed no symptoms.
- ARIA were generally mild or moderate in radiographic severity and were transient.
- Radiographic severity and symptomatic status were similar for ApoE ε4 carriers and noncarriers.
- Radiographic severity of ARIA alone is not predictive of symptomatic status.
- Radiographically severe ARIA-H was generally concurrent with ARIA-E.
- New-onset symptoms were noted in ≈6% of ARIA events where dosing was continued.

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Introduction

- Aducanumab is a human, immunoglobulin γ1 mAb directed against aggregated soluble and insoluble forms of Aβ.[1]
- Aducanumab is the first FDA-approved Alzheimer's disease treatment that reduces Aβ plaques, a defining pathophysiological feature of Alzheimer's disease.[2]
- ARIA, a spectrum of imaging findings detected on brain MRI, are associated with the use of Aβ-targeting mAbs, including aducanumab, in patients with Alzheimer's disease.[1,3]
  - ARIA-E refers to brain vasogenic edema or sulcal effusion detected on FLAIR imaging sequences.[3,4]
  - ARIA-H refers to brain microhemorrhages or localized superficial hemosiderosis detected on GRE/T2* sequences.[3,4]
- EMERGE (NCT02484547) and ENGAGE (NCT02477800) were Phase 3 studies that evaluated the efficacy and safety of aducanumab in patients with early Alzheimer's disease.[5,6]

Methods

- A pooled EMERGE and ENGAGE safety data set of participants randomized to either placebo or the high-dose aducanumab was analyzed to investigate overall characteristics of ARIA within the trials.
- ARIA risk-minimization strategies in the studies included dose titration, routine brain MRI monitoring, ad hoc MRI testing as clinically indicated, and possible dose suspension or permanent discontinuation among patients who developed ARIA.
  - Routine brain MRI scans were performed at baseline and Weeks 14, 22, 30, 42, 54, 66, 78, 94, 102, 110, 122, 134, 158, 182, and 198 (follow-up) (**Figure 1**).
  - The criteria for dose suspension or discontinuation were based on the radiographic severity of ARIA and the presence of clinical symptoms (**Table 1**).
- On detection of an ARIA episode, follow-up MRIs were conducted approximately every 4 weeks to document radiographic resolution of ARIA-E or stabilization (ie, no change on 2 consecutive MRIs) of ARIA-H.

Results

- A pooled EMERGE and ENGAGE safety data set consisted of 1105 participants in the aducanumab 10 mg/kg group and 1087 participants in the placebo group.
- In the 10 mg/kg group, ARIA-E was the most common adverse event (35%), with a higher incidence observed in ApoE ε4 carriers compared with noncarriers (42% vs. 20%, respectively) (**Table 2**).
  - ARIA-E and ARIA-H were frequently concurrent, and the incidence of isolated ARIA-H was similar to that with placebo.
  - The incidence of CNS hemorrhage >1 cm was balanced between the placebo and the 10 mg/kg groups.
  - 10% of participants in the 10 mg/kg group had recurrent ARIA-E.
  - There were no fatal events due to ARIA.
- The majority of first ARIA-E events occurred within the first 8 doses of aducanumab treatment, particularly during titration (**Figure 1**).
  - ≈50% of first ARIA-E occurred prior to dose 7 (Week 24), and 90% occurred prior to dose 12 (Week 44).
- Radiographic severity of ARIA-E was characterized as mild (30%), moderate (58%), or severe (13%) (**Table 3**).
  - 98% of ARIA-E resolved on MRI during the studies, including 68% by Week 12 and 91% by Week 20.
  - 76% of aducanumab-treated participants with ARIA showed no symptoms.
  - 24% of participants with ARIA reported symptoms, typically characterized as mild or moderate.
    - The most frequent symptom of ARIA was headache (reported in 13% of participants with ARIA).
    - Other frequent symptoms were confusion (5%), dizziness (4%), visual disturbance (2%), and nausea (2%).
- Regardless of radiographic severity of the event, most ARIA events were asymptomatic (**Table 4**).
- For events of radiographically severe ARIA-H microhemorrhage and superficial siderosis, 83% and 92%, respectively, were concurrent with ARIA-E (**Table 5**).
- For most events that began as mild on MRI and asymptomatic, among participants who continued dosing 6% became symptomatic and radiographic worsening was seen in 40% (**Table 6**).
  - For events that became moderate or severe on MRI, most did so within 4 or 8 weeks (55% and 26%, respectively) of initial detection of ARIA-E.

Table 1: Disposition of ARIA cases

Clinical symptom severity	Severity on MRI[2]		
	Mild	Moderate	Severe
ARIA-E			
Asymptomatic	Continue dosing at current dose and schedule	Suspend dosing[a]	
Symptomatic	Suspend dosing[a]		
Serious	Discontinue dosing		
ARIA-H			
Asymptomatic	Continue dosing at current dose and schedule	Suspend dosing[a]	Discontinue dosing
Symptomatic	Suspend dosing[a]		
Serious	Discontinue dosing		

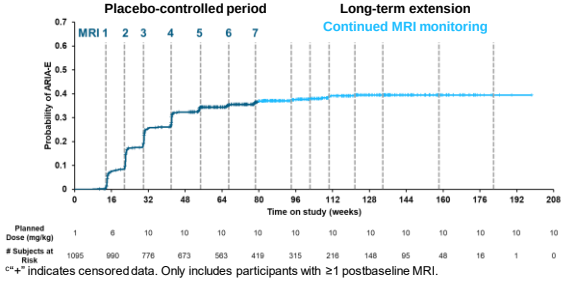
[a]After radiographic resolution (ARIA-E) or stabilization (ARIA-H) and resolution of symptoms (if present), the participant may resume dosing at the same dose and titration schedule.

Table 2: Incidence of ARIA in EMERGE and ENGAGE

	Placebo n=1087	Aducanumab 10 mg/kg n=1105
Any ARIA, n (%)	111 (10)	454 (41)
ARIA-E, n (%)	29 (3)	387 (35)
ApoE ε4 carriers, n/N (%)	16/747 (2)	315/749 (42)
ApoE ε4 noncarriers, n/N (%)	13/340 (4)	72/356 (20)
ARIA-H, n (%)	94 (9)	312 (28)
ARIA-H microhemorrhage, n (%)	71 (7)	212 (19)
ARIA-H superficial siderosis, n (%)	24 (2)	162 (15)
CNS hemorrhage >1 cm, n (%)	4 (<1)	6 (<1)
Concurrent ARIA-E and ARIA-H, n (%)	12 (1)	233 (21)
Isolated ARIA-H, n (%)[b]	82 (8)	67 (6)
Recurrent ARIA-E, n (%)	0	113 (10)

[b]ARIA-H in participants who did not have ARIA-E.

Figure 1: Timing of first ARIA-E[c]



[c]"+" indicates censored data. Only includes participants with ≥1 postbaseline MRI.

Table 3: Radiographic and symptomatic severity of ARIA

	Placebo n=1087	Aducanumab 10 mg/kg ApoE ε4 carrier n=749	Aducanumab 10 mg/kg ApoE ε4 noncarrier n=356	Aducanumab 10 mg/kg Total n=1105
Number of patients with ARIA-E, n	29	315	72	387*
Mild on MRI, n (%)	21 (72)	93 (30)	22 (31)	115 (30)
Moderate on MRI, n (%)	8 (28)	181 (57)	42 (58)	223 (58)
Severe on MRI, n (%)	0	41 (13)	8 (11)	49 (13)
Number of patients with any ARIA: Worst symptomatic status, n	111	359	95	454
Asymptomatic, n (%)	106 (95)	267 (74)	77 (81)	344 (76)
Symptomatic, n (%)[d]	5 (5)	92 (26)	18 (19)	110 (24)
Mild, n (%)	3 (3)	59 (16)	13 (14)	72 (16)
Moderate, n (%)	1 (<1)	27 (8)	2 (2)	29 (6)
Severe, n (%)	1 (<1)	3 (<1)	2 (2)	5 (1)

[d]Symptomatic severity of an ARIA episode is the maximum severity of symptoms experienced by a participant during the event. Severity is missing if none of the reported symptoms overlapped with the radiographic duration of the ARIA event. *% totals may not add to 100 due to rounding.

Table 4: Relationship between radiographic severity and symptomatic status of ARIA

	Placebo n=1087	Aducanumab 10 mg/kg n=1105
Number of ARIA events: Mild on MRI, n	126	484
Asymptomatic, n (%)	123 (98)	405 (84)
Symptomatic, n (%)	3 (2)	79 (16)
Number of ARIA events: Moderate on MRI, n	14	407
Asymptomatic, n (%)	11 (79)	342 (84)
Symptomatic, n (%)	3 (21)	65 (16)
Number of ARIA events: Severe on MRI, n	5	124
Asymptomatic, n (%)	5 (100)	90 (73)
Symptomatic, n (%)	0	34 (27)

Table 5: Timing of radiographically severe ARIA-H relative to that of ARIA-E

	Aducanumab 10 mg/kg n=1105
Number of MRI-severe ARIA-H microhemorrhage events, n	35
Not concurrent with ARIA-E, n (%)	6 (17)
Concurrent with ARIA-E, n (%)	29 (83)
Detected at same time as ARIA-E, n (%)	15 (43)
Detected on follow-up for ARIA-E, n (%)	12 (34)
Concurrent ARIA-E was MRI moderate or severe, n (%)	29 (83)
Number of MRI-severe ARIA-H superficial siderosis events, n	38
Not concurrent with ARIA-E, n (%)	3 (8)
Concurrent with ARIA-E, n (%)	35 (92)
Detected at same time as ARIA-E, n (%)	22 (58)
Detected on follow-up for ARIA-E, n (%)	12 (32)
Concurrent ARIA-E was MRI moderate or severe, n (%)	31 (82)

Table 6: Continued dosing for radiographically mild, asymptomatic ARIA-E

	Aducanumab 10 mg/kg n=1105
Total number of ARIA-E events that began as mild on MRI and asymptomatic and were treated with ≥1 dose, n	172
Event remained mild on MRI and asymptomatic, n (%)	100 (58)
Event changed, n (%)	72 (42)
Became symptomatic, n (%)	11 (6)
Became moderate or severe on MRI, n (%)	69 (40)
Moderate on MRI, n (%)	68 (40)
Severe on MRI, n (%)	1 (1)

Abbreviations Aβ, amyloid beta; ApoE, apolipoprotein E; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema; ARIA-H, ARIA-microhemorrhages, macrohemorrhages, or superficial siderosis; CNS, central nervous system; FDA, US Food and Drug Administration; FLAIR, Fluid-attenuated inversion recovery; GRE, gradient recalled echo; mAb, monoclonal antibody; MRI, magnetic resonance imaging.

References 1. Sevigny J, et al. *Nature*. 2016; 537:50–56; 2. Aduhelm. Prescribing information. Biogen, Inc.; 2021.; 3. Sperling RA, et al. *Alzheimers Dement*. 2011;7:367–385. 4. Barakos J, et al. *AJNR Am J Neuroradiol*. 2013;34:1958–1965. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/ 5. NCT02484547; 6. NCT02477800. Accessed July 9, 2021.

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