Prevalence of asymptomatic vasogenic edema in pretreatment Alzheimer's disease study cohorts from phase 3 trials of semagacestat and solanezumab

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Abstract

Background: Cerebral vasogenic edema (VE) has been reported to occur during antiamyloid immunotherapy. VE may be associated with central nervous system pathology with blood–brain barrier disruptions; however, less is known about the prevalence of naturally occurring VE in patients with Alzheimer's disease (AD).

Methods: Fluid-attenuated inversion recovery imaging sequences were obtained from four ongoing multicenter, randomized, double-blind, placebo-controlled, phase 3 trials in patients with mild-to-moderate AD. The first set of baseline scans was from patients in volumetric magnetic resonance imaging addenda in the Interrupting Alzheimer's Dementia by EvaluatiNg Treatment of Amyloid PathologY (IDENTITY) studies examining semagacestat, a γ-secretase inhibitor (cohort 1, n = 621). The second set of baseline scans was from the EXPanding alzhEimer's Disease InvestigaTIONs (EXPEDITION) studies examining solanezumab, an anti-Aβ monoclonal antibody (cohort 2, n = 2141). Readers were blinded to patient-identifying information and future treatment. A third set of baseline scans was from the first 700 patients who underwent protocol-specified magnetic resonance imaging before randomization in the EXPEDITION studies (cohort 3). The analysis used three neuroradiologists: two performed independent primary interpretations and the third was the adjudicator. Readers were blinded to patient information, treatment, protocol, and time point.

Results: Four cases of asymptomatic VE were detected at baseline/screening. Two VE cases were due to underlying extra-axial mass lesions. The third VE case was associated with numerous microhemorrhages in keeping with cerebral amyloid angiopathy-related inflammation or Aβ-related angiitis. The final VE case demonstrated localized sulcal fluid-attenuated inversion recovery imaging hyperintensity. No VE was detected in cohort 3 by readers blinded to patient baseline status.

Conclusions: VE seems to be rare at baseline in patients with AD in clinical trials, 2 of 2762 associated with AD. Additional cohorts should be evaluated to support these findings.
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Keywords: Alzheimer's disease; Clinical trials; Magnetic resonance imaging; Vasogenic edema; Cerebral microhemorrhage

1. Introduction

To date, two magnetic resonance imaging (MRI) findings have been shown to occur in a minority of patients treated with therapies that target β-amyloid (Aβ): vasogenic edema (VE) and microhemorrhages (MHs) [1]. VE is a term that generally describes increased permeability of the vascular

bed, leading to leakage of fluid into the cerebral parenchymal extracellular space [2]. VE is typically a transient and reversible process, and in milder cases it may be clinically asymptomatic. In the clinical setting, the majority of detected VE is the result of a variety of definable underlying conditions, such as neoplasm and infectious conditions, including abscess and cerebritis. VE may also be encountered in less common conditions, such as vasculitis and posterior reversible encephalopathy syndrome (PRES) [3,4]. The prevalence of MH has been described in numerous different natural history studies representing a variety of settings [5]. MH is common in natural history studies of elderly patients with a prevalence rate in the range of 10% to 20%, and has a naturally occurring 2-year incidence rate of about 12% [6]. Therefore, all incident MHs in a therapeutic trial cannot be ascribed to treatment. In contrast, the naturally occurring prevalence of VE in elderly patients, although thought to be extremely low, has not been formally described. The goal of this study was to ascertain the prevalence of VE in patients diagnosed with Alzheimer's disease (AD) who had been recruited for therapeutic interventional trials. VE prevalence was established on baseline MRI in patients with AD who had not yet started treatment. Our data, therefore, establish a benchmark prevalence rate for this condition in patients who might be recruited for clinical trials.

2. Methods and materials

Baseline (prestudy treatment) MRI scans were obtained from patients entering four ongoing trials of therapies that target Aβ being studied for the treatment of AD. All patients were diagnosed with mild-to-moderate probable AD (met National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria), and inclusion/exclusion criteria included evaluation of a computed tomographic or an MRI scan obtained within 2 years to exclude reasons for dementia other than AD (stroke, Modified Hachinski scale score of ≤4; depression, Geriatric Depression scale score of ≤6; vascular dementia, did not meet National Institute of Neurological Disorders and Stroke/Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria). Patients were not excluded because of the presence of MH in most countries participating in the studies, except for the United Kingdom and France, where patients with more than two MHs were excluded. Patients meeting these general inclusion criteria subsequently underwent a protocol-specified MRI before randomization to determine the presence of VE and the number and size of pre-existing MHs before treatment (baseline). Protocols were reviewed and approved by institutional review boards, and all patients and caregivers provided written informed consent. Two of the trials (H6L-MC-LFAN, Interrupting Alzheimer's Dementia by EvaluatiNg Treatment of Amyloid PaThologY [IDENTITY]; and H6L-MC-LFBC, IDEN-

TITY2) were studying semagacestat, a γ-secretase inhibitor, and the other two trials (H8A-MC-LZAM, EXPanding alzhEimer's Disease InvestigaTIONs [EXPEDITION]; and H8A-MC-LZAN, EXPEDITION2) are currently studying the anti-Aβ monoclonal antibody solanezumab.

Study H6L-MC-LFAN (IDENTITY) is a multicenter, randomized, double-blind, placebo-controlled, phase 3 study comparing daily doses of 100 mg or 140 mg semagacestat with placebo in 1536 patients with mild-to-moderate AD. Study H6L-MC-LFBC (IDENTITY2) is a multicenter, randomized, double-blind, placebo-controlled, phase 3 study comparing daily doses of 140 mg semagacestat with placebo in 1111 patients with mild-to-moderate AD. Further details can be found for the IDENTITY trials at http://clinicaltrials.gov/ct2/show/NCT00594568?term=LFAN&rank=2 and http://clinicaltrials.gov/ct2/show/NCT00762411?term=LFBC&rank=2, respectively.

Studies H8A-MC-LZAM (EXPEDITION) and H8A-MC-LZAN (EXPEDITION2) are multicenter, randomized, double-blind, placebo-controlled, phase 3 studies in patients with mild-to-moderate AD (n = 1012 and 1040, respectively) receiving monthly infusions of 400 mg solanezumab or placebo. Further details can be found for the EXPEDITION trials at http://clinicaltrials.gov/ct2/show/NCT00905372?term=LZAM&rank=2 and http://clinicaltrials.gov/ct2/show/NCT00904683?term=LZAN&rank=2, respectively.

The first set of baseline scans was obtained from a subset of patients (cohort 1, n = 621) who agreed to participate in an optional volumetric MRI (vMRI) study addenda regardless of whether they were randomized to treatment or subsequent screen failures (n = 28) in the IDENTITY trials. These vMRI addendum participants were similar to the overall IDENTITY population. A single reader (J.B.) was blinded to all patient-identifying information and future treatment status (investigational drug versus placebo), but not to the fact that scans were performed at baseline.

The second set of baseline scans was obtained from patients participating in the EXPEDITION studies with evaluable MRIs (cohort 2, n = 2141). Of these patients, 121 were subsequent screen failures. Readers were blinded to all patient-identifying information and future treatment status (investigational drug versus placebo), but not to the fact that scans were obtained at baseline.

Because VE is thought to occur in association with pathological conditions or during treatment with therapies that target Aβ, our objective was to determine whether reader bias, resulting from knowing that scans were obtained at baseline, could influence the interpretation of scans. To evaluate this potential bias, a third set of baseline scans was reanalyzed in a blinded manner. Only in this analysis were readers blinded to time point (baseline versus post-treatment visit), in addition to all patient-identifying information, treatment status (investigational drug versus placebo), protocol, and examination date.

This set of scans (cohort 3) was a subset of the scans from the patients in cohort 2 and was obtained from the first 700 patients who received a protocol-specified MRI before randomization in the EXPEDITION trials. Of these patients, 41 were subsequent screen failures. These scans were reread by two neuroradiologists (Erik Gaensler, Camilla Lindan), with the third neuroradiologist (J.B.) serving as the adjudicator. These neuroradiologists were instructed that scans could be obtained either at baseline or after randomization in a clinical trial using a therapy putatively targeting Aβ, thus precluding bias associated with knowing that the scans were obtained at baseline.

The three neuroradiologists have extensive experience in the assessment of VE. All work at major medical centers with solid organ transplant and high-volume oncology and birthing programs (risk factors for PRES), thus commonly encountering various degrees of VE and PRES. They have also served as drug trial central readers for more than 15 immune and nonimmune antiamyloid therapy trials, and have observed and evaluated VE across three different programs of therapies that target Aβ.

For all three cohorts, each scan was interpreted independently, and no comparisons with other time points were made. Fluid-attenuated inversion recovery (FLAIR) imaging sequences were evaluated for the presence of edema presenting either within the brain parenchyma or as sulcal FLAIR hyperintensity, and distinct from potential mimics such as tissue gliosis or sulcal subarachnoid hemorrhage, respectively [3]. T2*-weighted gradient refocused echo sequences were obtained and evaluated for the presence of MHs, characterized as small areas of signal void with associated blooming, and distinct from potential mimics such as vessel flow voids [7].

Given that the study population consisted of patients from four trials, MRI was obtained at approximately 273 imaging centers across the world. Site training for MRI standardization was performed. Given the multisite nature of this study, imaging was conducted on a wide range of imaging platforms, including three MR vendors (Siemens, General Electric, and Philips) and one of two MRI field strengths, 1.5 or 3.0 T (Table 1). Two-dimensional FLAIR protocol was harmonized across manufacturer and field strength with range of values: echo time = 94 to 140 ms; inversion time =

2200 to 2800 ms; repetition time = 9000 to 10,000 ms; slice thickness = 5 mm with 1-mm gap.

Because these analyses were conducted on baseline data from unlocked, unvalidated databases from ongoing clinical trials, minor changes in some of the demographic data may occur on subsequent data lock.

3. Results

Demographic data for the three patient cohorts are presented in Table 2. The ages and Mini-Mental State Examination scores are typical of those seen in clinical trials of mild-to-moderate AD.

Four cases of asymptomatic VE were detected at baseline/ screening from the three cohorts. Two cases of VE were detected in the baseline scans of patients participating in the vMRI addenda from the IDENTITY studies (cohort 1); these were associated with extra-axial mass lesions (meningioma and giant geniculate ganglion schwannoma). Because these two cases of VE were associated with clearly demonstrable underlying pathology, namely brain tumors, the VE was not considered idiopathic. However, the remaining two VE cases were potentially spontaneous or idiopathic. One of these cases was detected at baseline in a patient who did not meet inclusion criteria in EXPEDITION (cohort 2). This case of VE was associated with numerous MHs, with overall imaging features consistent with cerebral amyloid angiopathy-related inflammation or Aβ-related angiitis [4,8–11]. These scans showed areas of FLAIR hyperintensity (Fig. 1A) in association with marked parenchymal MHs and siderosis (Fig. 1B). The final case of VE presented as a sulcal focus of FLAIR hyperintensity (Fig. 2A). No associated T1 or T2 shortening on susceptibility-weighted imaging was evident to suggest that this finding represented a blood product. Additionally, no associated blooming or susceptibility artifact was evident to suggest that this finding may represent an artifact. No MH or siderosis that could be indicative of cerebral amyloid angiopathy was detected in this patient's baseline scan. The patient returned for follow-up imaging 4 weeks later, and the VE was no longer evident (Fig. 2B). No report of any such similar finding, which could be construed as an artifact, had been previously noted on this particular MR scanner.

Table 1
MRI scanner specifics and patient numbers

	Cohort 1, n = 621	Cohort 2, n = 2141	Cohort 3, n = 700
	IDENTITY vMRI patients	EXPEDITION baseline patients	EXPEDITION adjudicated patients
MRI field strength, number of patients	1.5 T, 621	1.5 T, 1757 3.0 T, 384	1.5 T, 597 3.0 T, 103
MRI manufacturer, number of patients	General Electric, 278 Siemens, 195 Philips, 148	General Electric, 782 Siemens, 845 Philips, 494 Toshiba, 20	General Electric, 265 Siemens, 265 Philips, 169 Toshiba, 1

Abbreviations: MRI, magnetic resonance imaging.

Table 2
Demographic data

	Cohort 1, n = 621	Cohort 2, n = 2141	Cohort 3, n = 700
	IDENTITY vMRI patients	EXPEDITION baseline patients	EXPEDITION adjudicated patients
Age, years	74.3 ± 8.0	75.0 ± 9.2	74.9 ± 9.0
Sex, % male	49	44	46
MMSE	21.3 ± 3.1	20.9 ± 3.1	20.9 ± 3.1
Race, %			
Caucasian	87.9	80.5	81.1
African American	1.3	2.8	4.1
Asian	7.6	16.1	14.1
Hispanic	3.2	NA	NA
Other	NA	0.6	0.6

Abbreviations: vMRI, volumetric magnetic resonance imaging; MMSE, Mini-Mental State Examination; IDENTITY, Interrupting Alzheimer's Dementia by EvaluatiNg Treatment of Amyloid PatHologY; EXPEDITION, EXPanding alzhEimer's Disease InvestigaTIONs.

No cases of VE were detected in the third cohort of the first 700 patients who received a protocol-specified MRI before randomization in the EXPEDITION studies by the neuroradiologists blinded to time point (baseline versus follow-up). No adjudication was necessary. This analysis suggests that readers knowing that scans were obtained at baseline in the original assessment did not bias the detection of VE.

4. Discussion

This analysis, in addition to the single case of VE that occurred in the absence of central nervous system pathology, suggests that the prevalence of VE in untreated patients in AD clinical trials is very rare.

With the report of VE occurring in the setting of clinical trials of therapies that target Aβ [2], the question arises as to whether a background prevalence of such a condition, namely VE without an underlying definable cause other than AD, exists in this population. To this end, we employed a team of neuroradiologists, specifically trained and sensitized to the detection of VE, to review baseline (prestudy drug) MRI scans of a large group of patients with AD to assess the background prevalence of VE with an appearance consistent with VE related to therapies that target Aβ. An important substudy was an evaluation of VE by readers who were blinded to whether the scans were obtained before or after initiation of therapy.

In this study, two cases of asymptomatic VE (not associated with an underlying mass lesion) were identified from 2677 screening/baseline scans of AD trial patients. Based on the MRI appearance combined with clinical history (which excluded any underlying clinical condition that would predispose the patient to PRES-like condition or infection/cerebritis), one case of VE was presumably related to angiitis associated with cerebral amyloid angiopathy [4,8–11]. This diagnosis was made on the basis of the characteristic imaging features of associated parenchymal MHs and sulcal siderosis. The second case of VE presented as an isolated sulcal focus of FLAIR hyperintensity. No associated T1 or T2 shortening on susceptibility-weighted imaging was evident to suggest that this finding represented a blood product, for example, subarachnoid hemorrhage. Additionally, no
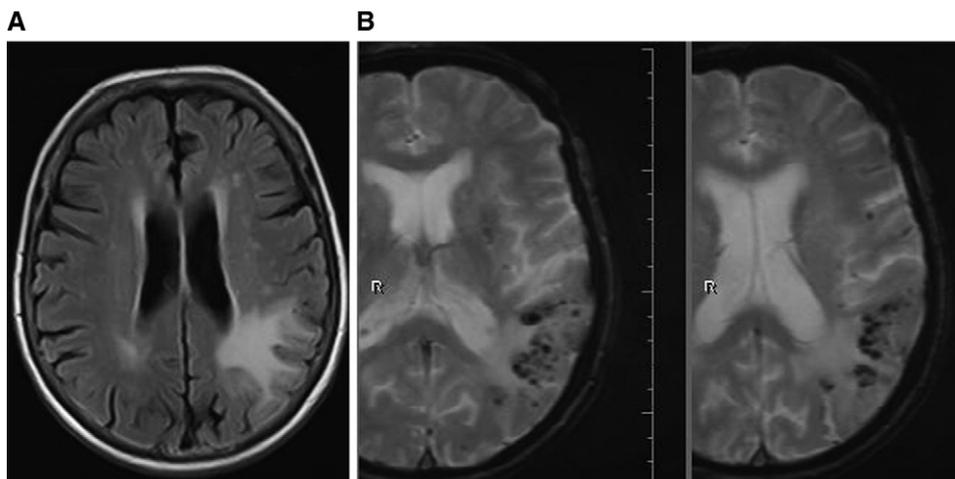

Fig. 1. Baseline axial fluid-attenuated inversion recovery images (A) reveal area of parenchymal hyperintensity in the left parietal lobe. Corresponding gradient refocused echo image (B) demonstrates extensive associated microhemorrhages.
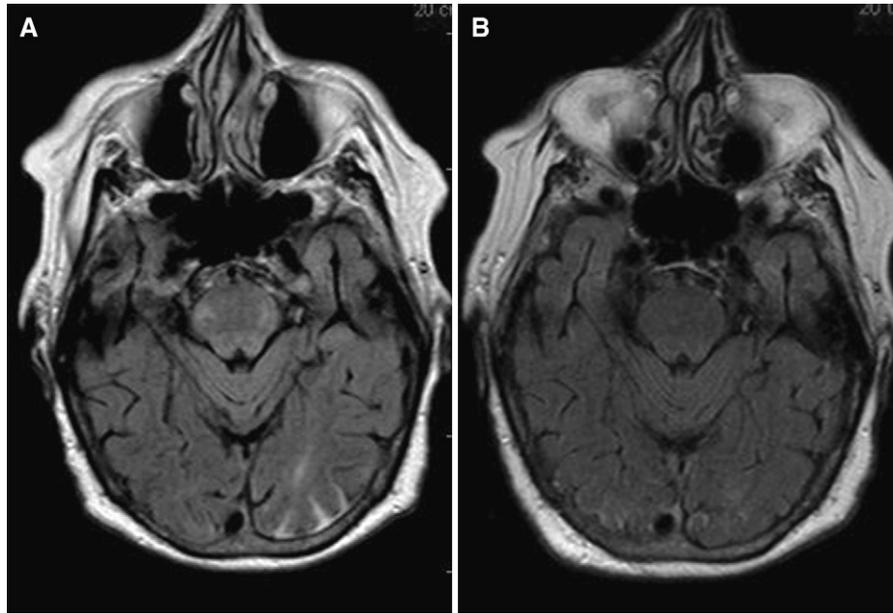
Fig. 2. Baseline axial fluid-attenuated inversion recovery images (A) reveal sulcal hyperintensity overlying the left occipital pole. Findings resolved on repeat imaging (B) at 4 weeks.

associated blooming or susceptibility artifact was evident to suggest that this finding may represent an artifact. These findings were no longer evident when the patient returned for repeat imaging 4 weeks later. Although an unexplainable artifact cannot be entirely excluded as the cause for this finding, this case raises the possibility of a transient occurrence of VE in a patient with AD.

Note that these two cases illustrate two very different appearances of VE. Although histological confirmation is obviously not available, the MRI intensity findings suggest mechanisms for these findings. The first case illustrates edema in the parenchyma, presumably from leakage of intravascular fluid into the parenchymal compartment due to compromise of the vessel wall (Fig. 1A). The second case illustrates what is consistent with proteinaceous fluid confined to the subarachnoid space in several sulci of the left occipital lobe (Fig. 2A). The high signal intensity on FLAIR in this case can be explained by vascular exudate with protein content high enough to shorten T1 relaxation in comparison with adjacent cerebrospinal fluid.

Pathologically proven cases of Aβ-related angiitis [6,8–10], also referred to as cerebral amyloid angiitis-related inflammation [4,7–11], have shown pathophysiology suggestive of T-cell and endothelial cell activation with leukocyte trafficking and cerebral vasoconstriction. Additionally, these findings of inflammation have histological features "suggesting immune-clearance of parenchymal Aβ" [11,12]. These observations provide insight into a proposed mechanism of spontaneous VE associated with AD, namely the possibility of amyloid movement from parenchyma to perivascular regions.

Although the neuroradiologists evaluating scans in this study are highly experienced, the knowledge that scans were obtained before initiation of treatment could have induced some degree of bias into scan interpretations. In this study, cohort 3 was evaluated with the readers blinded to the timing of the scans, that is, before or after initiation of treatment. Although limited by a sample size of only 700, the lack of any reports of VE in this cohort by blinded readers suggests that reader bias did not greatly influence the overall results of this study of baseline scans.

The incidence of spontaneous VE in the general AD population could be greater than described in our study because of the exclusion of subjects with known extensive cerebral amyloid angiopathy or vascular component to their AD or other clinical reasons (laboratory values, medical history or conditions) before the protocol-specified scan in our studies. Patients who underwent the protocol-specified MRI had been previously evaluated using the aforementioned inclusion/exclusion criteria. Thus, the patients who were evaluated with the protocol-specified MRI are likely to be similar to those entering clinical trials for AD more generally.

With the report of VE related to therapies that target Aβ, an understanding of the prevalence of VE in untreated patients with AD is important. In this analysis, we evaluated the background prevalence of VE in AD study population cohorts totaling 2762 patients. In this cohort, two cases of VE were identified as being tumor related. The actual prevalence of spontaneous VE was only 2 of 2762 in this sample. The blinding of readers to baseline time point did not result in the detection of any new cases of VE not found in the initial reading. Taken together, these findings suggest that VE, as reported in trials that target Aβ, does occur spontaneously, but is uncommon in untreated patients with AD.

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