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LETTER

Don't forget primary progressive aphasia for anti-amyloid drugs: An estimation of eligible patients from the Lausanne Memory Center registry

Dear Editor,

We read with great interest the results of the phase III Clarity AD trial, on the clinical relevance of lecanemab in patients with early Alzheimer's disease (AD).[1] Its subsequent approval by the Food and Drug Administration raises the question of its implementation in clinical practice. While this phase III trial enrolled only typical, that is, amnestic AD patients,[1] two other common AD phenotypes are well established,[2] including primary progressive aphasia (PPA). Non-amnestic AD should also benefit from the disease-modifier effect of lecanemab. If many projections on how many amnestic patients could benefit from this treatment,[3–5] no precise estimation exists on the subgroup of AD patients with PPA presentation.

We therefore performed a 10-year retrospective analysis on PPA patients from the Leenaards Memory Center in Lausanne, Switzerland,[6] from 2013 to 2023, and identified, based on the inclusion and exclusion criteria of the Clarity AD trial,[1] the number of PPA patients (all phenotypes combined) that could benefit from lecanemab treatment.

This analysis was granted a waiver by the local ethics commission.

We identified 54 patients who met consensus diagnostic criteria for PPA.[7] Eighteen (33%) patients presented a logopenic variant (lvPPA), 21 (39%) a semantic variant (svPPA), and 11 (20%) a non-fluent variant (nfvPPA; Table 1). Four (7%) patients did not fulfill criteria for any specific variant despite meeting core criteria for PPA and were classified as mixed/unclassifiable (PPA-M/U; Table 1).

Thirty-two (59%) have a global Clinical Dementia Rating (CDR) score of 0.5 and their mean Mini-Mental State Examination (MMSE) ranges from 20.2 to 25.5, depending on the variants (Table 1).

Investigations performed combined 31 lumbar punctures, 3 ^{18}F-flutemetamol amyloid positron emission tomography (PET), and 6 ^{18}F-AV-1451 tau PET, leading to an amyloid status in 34 (63%) patients and a complete amyloid/tau/neurodegeneration status in 30 (56%) patients. These workups demonstrated positive AD biomarkers in 19 (38%) patients, as expected, mostly in patients with lvPPA (14, 26% of total PPA, 78% of lvPPA), but also in patients with other phenotypes (2 svPPA, 2 nfvPPA, and 1 PPA-M/U; Table 1). Other diagnoses are frontotemporal lobar degeneration, progressive supranuclear palsy, and corticobasal degeneration.

Applying the inclusion/exclusion Clarity AD criteria, with the exception of memory impairment, to this set of PPA patients identified 11 out of 54 (20%) eligible patients, mostly lvPPA patients (8, 15% of total PPA) and 1 patient in each other subgroup. Interestingly, if 44% of lvPPA patients would be eligible for lecanemab treatment at time of diagnosis in our cohort, 57% of lvPPA with positive AD biomarkers would fulfil these modified criteria. We should acknowledge that we did not perform AD biomarkers in four lvPPA patients, but presumably, applying the 44% eligibility observed, one or two of them would have been potential candidates.

Our findings regarding the frequency of AD diagnosis in the different PPA presentations are in line with the published neuropathological data, in which 80% of lvPPA cases fulfil a neuropathological diagnosis of AD, while the other variants are seldom AD (8% for nfvPPA, 5% for svPPA, and 50% for PPA-M/U).[8] A potential bias might be the underrepresentation of lvPPA in our sample, because these patients often display other cognitive deficits[9] and are therefore sometimes identified as having a multi-domain cognitive impairment and not an aphasic predominant presentation, eluding the PPA inclusion criteria.[7] Finally, excluding potential candidates for lecanemab based on their MMSE score is questionable, because MMSE is heavily dependent on language skills.[10]

Nevertheless, this study provides evidence that 44% of lvPPA could benefit from lecanemab, excluding memory impairment as inclusion criteria from Clarity AD, and even more (57%) if they have positive AD biomarkers. Furthermore, while the other PPA variants are seldom clinico-biological AD, some of the patients with svPPA or nfvPPA might still benefit from this treatment, if the possibility of a co-pathology is clearly excluded. This study highlights the need for an extensive biomarker workup in PPA patients, following the most recent recommendations[2] as well as the need for trials of disease-modifying drugs in non-amnestic AD presentations.

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Alessa Hausmann and Paolo Salvioni Chiabotti contributed equally to this work.

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TABLE 1 Primary progressive aphasia at the Leenaards Memory Center.

	lvPPA ($n = 18$)	svPPA ($n = 21$)	nfvPPA ($n = 11$)	PPA-M/U ($n = 4$)	Total ($n = 54$)
Proportion of PPA, %	33	39	20	7	
Age at diagnosis, years	72.6 ± 8.5	63.1 ± 8.2	72.7 ± 8.9	68.4 ± 12.9	70.8 ± 6.2
Female sex, no. (%)	6 (33.3)	5 (23.8)	2 (18.2)	2 (50)	15 (27.8)
Global CDR score 0.5, no. (%)	13 (72)	12 (57)	6 (55)	1 (25)	32 (59)
Global CDR score ≥ 1, no. (%)	5 (23)	9 (41)	5 (23)	3 (14)	22 (41)
Mean MMSE score	20.2 ± 6.5	24.4 ± 4.1	22.9 ± 8.9	25.5 ± 2.5	22.7 ± 6.2
Positive AD biomarkers, no. (% total, % PPA variant)	14 (26, 78)	2 (4, 10)	2 (4, 18)	1 (2, 25)	19 (35)
Other, no. (% total, % PPA variant)	4 (7, 22)	19 (35, 90)	9 (17, 82)	3 (6, 75)	35 (65)
Lecanemab eligibility at diagnosis, no. (% total, % PPA variant)	8 (15, 44)	1 (2, 5)	1 (2,9)	1 (2,25)	11 (20)

Abbreviations: AD, Alzheimer's disease; CDR, Clinical Dementia Rating; lvPPA, logopenic variant primary progressive aphasia; MMSE, Mini-Mental State Examination; M/U, mixed/unclassifiable; nfvPPA, non-fluent variant primary progressive aphasia; PPA, primary progressive aphasia; svPPA, semantic variant primary progressive aphasia.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests. Author disclosures are available in the supporting information.

Alessa Hausmann
Paolo Salvioni Chiabotti
Mirco Nasuti
Olivier Rouaud
Gilles Allali

Leenaards Memory Center, Department of Clinical Neurosciences, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland

Correspondence
Paolo Salvioni Chiabotti, Leenaards Memory Center, Department of Clinical Neurosciences, Centre Hospitalier Universitaire Vaudois and University of Lausanne, 16, chemin de Mont-Paisible, 1011 Lausanne, Switzerland.
Email: paolo.salvioni@chuv.ch

ORCID

Alessa Hausmann https://orcid.org/0000-0003-3410-8266
Paolo Salvioni Chiabotti https://orcid.org/0000-0002-6745-0722

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