A Randomised, Controlled, Multicentre, International Study of the Impact of Florbetapir (^{18}F) PET Amyloid Imaging on Patient Diagnosis and Management

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ABSTRACT

Aim

To evaluate the impact of amyloid PET on diagnosis and patient management in a multicentre RCT.

Methods

Physicians identified patients seeking diagnosis for mild impairment or dementia, where Alzheimer's disease (AD) was considered a possible cause (<85% certain). The physician recorded a working diagnosis and a management plan. Patients underwent a florbetapir PET scan and were then randomised to immediate or delayed (1 year) feedback regarding amyloid status. Patients returned to the centre after 3 months and the physician updated the diagnosis and the management plan. This analysis examined the impact of immediate feedback vs. delayed feedback of amyloid status on diagnosis and management changes at 3 months.

Results

618 subjects were randomised to immediate or delayed amyloid PET feedback arms (308 vs. 310). 602 subjects completed 3 months. A significantly higher proportion of patients who received immediate feedback of amyloid status showed a change in diagnosis (98/301[32.6%] vs. 19/299[6.4%];p<0.0001). Significantly more patients receiving immediate feedback had a change in their management plan (204/300[68.0%] vs. 166/299[55.5%];p=0.0017), mainly driven by the modification in AD medications use.

Conclusions

This RCT supports the hypothesis that knowledge of amyloid status as determined by florbetapir PET imaging impacts diagnosis and alters patient management.

BACKGROUND

- Clinical diagnosis of Alzheimer's disease (AD) is only around 70% accurate[1,2], with approximately 20% of cases having no AD pathology at autopsy[3,4].
- Biomarkers of amyloid pathology can improve diagnostic accuracy[5] and assist in ruling in or ruling out AD when there is clinical uncertainty[1,5].
- Most of the evidence so far on the clinical utility of florbetapir comes from open-label studies in which physicians changed their **planned** management after a scan[6].
- We performed the first prospective, randomised controlled multicentre study to evaluate the impact of florbetapir amyloid Positron Emission Tomography (PET) imaging on diagnosis and management in patients with cognitive impairment suspected to be related to AD.

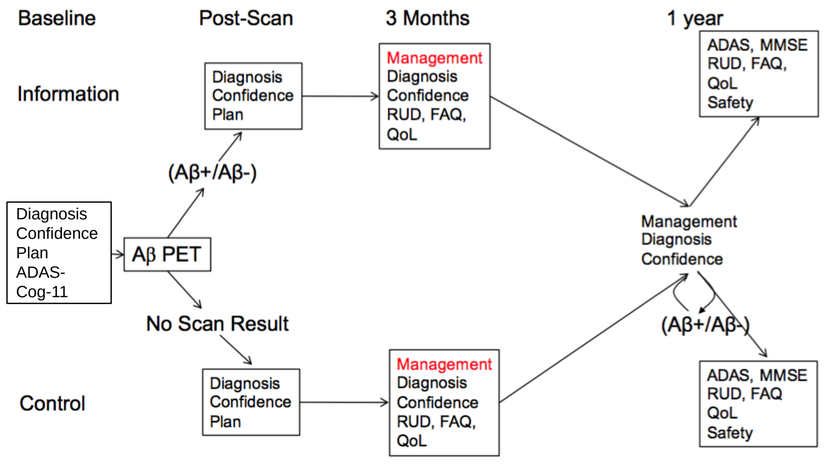
OBJECTIVE

- To determine whether knowledge of florbetapir PET amyloid status altered patient management
  - Hypothesis: The proportion of subjects with a change in management from baseline to 3 months will be greater for patients who receive PET scan results immediately (Information arm) vs. those who receive the scan result 12 months later (Control arm).

METHODS

- Randomised multicentre study (NCT01703702) conducted in France, Italy and the United States of America.
- Inclusion criteria:
  - Patients (aged 50–90 years) with evidence of late-life progressive cognitive decline (mild impairment or dementia with Mini-Mental State Examination [MMSE] score ≥16)
  - Cause of impairment <85% certain but AD ≥15% likely
  - Diagnostic evaluation for cognitive decline completed within 18 months prior to enrolment or ongoing.
- Exclusion criteria:
  - Known brain lesion, pathology or alternative diagnosis
  - Patients under the care of a physician solely for the purpose of a trial.
- Patients underwent florbetapir amyloid PET imaging within 30 days of baseline evaluation.
- Patients were randomised to receive PET scan results immediately (Information arm) or 12 months later (Control arm). The study design and analyses performed are summarised in Figure 1.
- Follow-up visits were conducted at 3 months and 12 months post-baseline.
- The study was approved by relevant ethics committees and regulatory authorities. Study procedures and risks were explained in advance and written informed consent given by the patient or a legally authorised representative.

Figure 1. Study Design



Aβ, Amyloid beta; ADAS-Cog-11, 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale; FAQ, Functional Activities Questionnaire; MMSE, Mini-Mental State Examination; PET, Positron Emission Tomography; RUD, Resource Utilization in Dementia instrument; QoL, Quality of Life in Alzheimer's Disease

Statistical Analysis

- Pearson's chi-squared test was used to test whether the difference in the proportion of subjects with a change in management from the baseline plan to actual management 3 months post-baseline in the Information vs the Control group was statistically significant.
- The primary analysis population included all patients with evaluable data at the relevant time point.
- Subgroup analyses were conducted to evaluate potential difference between results in Aβ+ versus Aβ- patients.

RESULTS

Patient Demographics

- Of 641 enrolled patients, 618 were randomised (Table 1).
- The 3 month efficacy analysis population consisted of 602 patients (600 with evaluable data) and 560 patients completed the full 12 month study.

Table 1. Baseline Patient Demographics

Parameter		Information group (N=308)	Control group (N=310)	Total (N=618)
Country, n (%)	France	87 (50.0%)	87 (50.0%)	174 (28.2%)
	Italy	109 (49.3%)	112 (50.7%)	221 (35.8%)
	USA	112 (50.2%)	111 (49.8%)	223 (36.1%)
Age (years), mean (SD)		73.1 (8.20)	72.7 (7.94)	72.9 (8.07)
Female, n (%)		142 (47.0%)	160 (53.0%)	302 (48.9%)
Education (years), mean (SD)		12.2 (4.38)	12.1 (4.59)	12.1 (4.49)
Aβ positive status, n (%)		192 (62.3%)	201 (64.8%)	393 (63.6%)
ADAS-Cog-11 score, mean (SD)		15.9 (8.18)	16.1 (9.12)	16.0 (8.66)
MMSE score, mean (SD)		24.0 (3.64)	23.9 (3.98)	23.9 (3.81)

Aβ, amyloid beta; ADAS-Cog-11, 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale; MMSE, Mini-Mental State Examination; SD, standard deviation; USA, United States of America.

Diagnosis Change at 3 Months

- A significantly higher proportion of patients in the Information group had a change in diagnosis (98 of 301 patients, 32.6%) versus the Control group (19 of 299 patients, 6.4%), p<0.0001.
- The difference between the groups was mainly due to cases where the scan result was in contradiction with the clinical diagnosis (Table 2):
  - In the Information group, most Aβ+ patients with a previous "Indeterminate" or "Not due to AD" diagnosis had their diagnosis changed to "Due to AD" whereas the opposite direction of diagnosis change was observed in Aβ- patients
  - This trend was not apparent in the Control group, whose diagnoses remained largely unchanged.

Table 2. Changes in Diagnosis at 3 Months, According to Aβ Status

Assigned group	Initial diagnosis	Post-scan diagnosis (at 3 months), n (%)		
		Due to AD	Indeterminate	Not due to AD
Aβ positive patients				
Control (N=194)	Due to AD (n=164)	159 (97.0%)	0 (0)	5 (3.1%)
	Indeterminate (n=8)	3 (37.5%)	5 (62.5%)	0 (0)
	Not due to AD (n=22)	1 (4.5%)	0 (0)	21 (95.5%)
Information (N=188)	Due to AD (n=155)	152 (98.1%)	1 (0.6%)	2 (1.3%)
	Indeterminate (n=8)	7 (87.5%)	1 (12.5%)	0 (0)
	Not due to AD (n=25)	23 (92.0%)	1 (4.0%)	1 (4.0%)
Aβ negative patients				
Control (N=105)	Due to AD (n=67)	62 (92.5%)	1 (1.5%)	4 (6.0%)
	Indeterminate (n=12)	1 (8.3%)	8 (66.7%)	3 (25.0%)
	Not due to AD (n=26)	1 (3.8%)	0 (0)	25 (96.2%)
Information (N=113)	Due to AD (n=65)	11 (16.9%)	1 (1.5%)	53 (81.5%)
	Indeterminate (n=13)	0 (0)	3 (23.1%)	10 (76.9%)
	Not due to AD (n=35)	0 (0)	0 (0)	35 (100%)

Aβ, amyloid beta; AD, Alzheimer's disease. Circled results indicate instances where results changed at 3 months in the Information (green circles) and Control (red circles) groups.

Management Plan Change at 3 Months

- The higher incidence of diagnosis change in the Information group was reflected in a higher proportion of patients undergoing changes in their management plan (Table 3), mainly driven by modifications to AD medication use.

Table 3. Changes in Management Plan at 3 Months

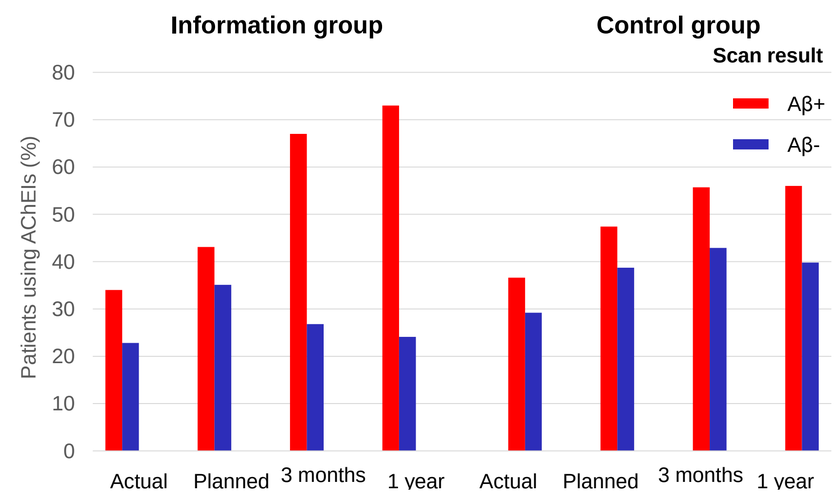
Parameter, n (%)	Information group (N=300*)	Control group (N=299)	P-value
Management plan change	**204 (68.0%)**	**166 (55.5%)**	**0.0017**
Change in indices that defined management plan at 3 months			
AD medication use (e.g. AChEI, memantine)	107 (35.7%)	66 (22.1%)	0.0002
Referral to specialists	90 (30.7%)	70 (23.4%)	0.0456
Neuropsychological testing	44 (14.7%)	29 (9.7%)	0.0631
Re-evaluation in 3 months	45 (15.0%)	42 (14.1%)	0.7406
Receipt of major diagnostic tests	63 (21.0%)	61 (20.4%)	0.8565

AChEI, acetylcholinesterase inhibitor; AD, Alzheimer's disease
**Data missing for 1 patient in the Information group (total group size at 3 months = 301).*

12-Month Outcomes

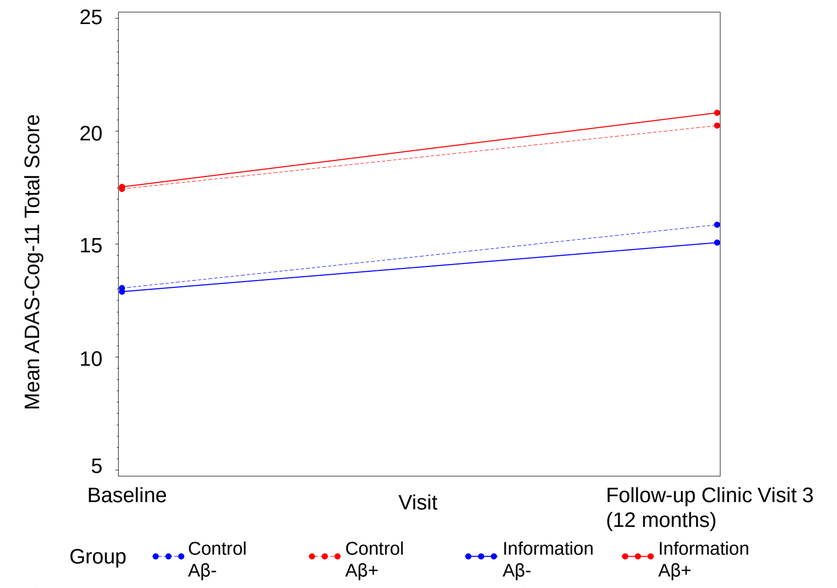
- The increased use of acetylcholinesterase inhibitors (AChEIs) at 3 months in the Information versus Control group was still observed at 12 months (Figure 2); the Information group also showed a greater difference in AChEI use between Aβ+ and Aβ- patients.
- No differences between the Information and Control groups were observed for:
  - cognitive change from baseline (according to the 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale [ADAS-Cog-11], the MMSE, or the Functional Activities Questionnaire)
  - resource use (Resource Utilization in Dementia instrument)
  - quality of life (QoL; QoL AD instrument)
- ADAS-Cog-11 scores were higher in Aβ+ versus Aβ- patients, but there was no difference between the change in ADAS-Cog-11 scores over 12 months between Information and Control groups, regardless of Aβ status (Figure 3).

Figure 2. Impact of Amyloid PET Information on the Prescription of AChEIs



Aβ, amyloid beta; AChEI, acetylcholinesterase inhibitor; PET, Positron Emission Tomography

Figure 3. Change in ADAS-Cog-11 Scores From Baseline to 12 Months, by Information Group and Amyloid Status



Aβ, amyloid beta; ADAS-Cog-11, 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale

Safety

- Reported treatment-emergent adverse events were unremarkable.
- There was no evidence that being randomised to the Information group versus the Control group was associated with increased psychological distress.

DISCUSSION

- This was the first randomised prospective study to look at the impact of amyloid imaging on diagnosis and actual patient management and outcomes.
- Diagnosis using standard National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria is reported to be only 70–80% reliable, and PET imaging provides additional information to aid diagnosis[1,5].
- Changes in diagnosis and patient management were greater in the group receiving immediate PET scan results than in the control group; this group difference in management was driven by AD medication changes, particularly acetylcholinesterase inhibitor use, when sorted by Aβ+ vs Aβ- status.
- Without amyloid imaging information, discordant diagnoses were not corrected in the large majority of cases, even after one year of clinical follow-up.

CONCLUSIONS

- This randomised study supports the hypothesis that knowledge of amyloid status as determined by florbetapir PET imaging impacts diagnosis and alters patient management.
- Without amyloid imaging information, the clinical follow-up appeared to be insufficient to correct discordant diagnoses.

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