Multicentre, Open-label, Randomised Study to Assess the Diagnostic Value of Amyloid PET Imaging in Patients with Subjective Cognitive Decline Plus, Mild Cognitive Impairment, or Dementia Where Alzheimer*s Disease Is in the Differential Diagnosis (Diagnostic and Patient Management Study)

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This study (AMYPAD Diagnostic and Patient Management Study) will determine in a real-life clinical setting for whom diagnostic amyloid PET imaging is appropriate, when this is best performed, and how the resulting information is influencing...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Encephalopathies
Study type	Observational invasive

Summary

ID

NL-OMON50470

Source
ToetsingOnline

Brief title
AMYPAD Diagnostic and Patient Management Study

Condition

- Encephalopathies
- Dementia and amnestic conditions

Synonym
amyloidosis, dementia

Research involving
Human

Sponsors and support

Primary sponsor: University of Geneva
Source(s) of monetary or material Support: Innovative Medicines Initiative 2 Joint undertaking under grant agreement No 115952. This Joint Undertaking receives support from the European Union□s Horizon 2020 research and innovation programme and EFPIA. ,GE Healthcare Ltd ,Janssen-Cilaq,Piramal Imaging Ltd

Intervention

Keyword: alzheimer's disease, amyloid, diagnostic work-up, PET

Outcome measures

Primary outcome

The difference, at 12 weeks after baseline, between the Early Amyloid PET arm

and the Late Amyloid PET arm in the proportion of patients for whom the

managing physician has made an etiologic diagnosis with very high confidence

(*90%). Diagnostic confidence will be measured with a visual analogue scale

(VAS) ranging from 0% (no confidence) to 100% (full confidence).

Secondary outcome

The timepoints are defined as follows: T0 = baseline, T1 = 12 weeks after T0,

T2 = 6 months (±14 days) after T0, T3 = 13 months (±4 weeks) after T0; T4 = *28

days after the second scan, which will be 12-18 months after T0. (All time

points are calculated relative to baseline.)

Diagnosis and Confidence

* The difference between the Early Amyloid PET arm and the Late Amyloid PET arm in the time (from baseline) to communicate a very-high-confidence (*90%) etiologic diagnosis to the patient.
* Change of etiologic diagnosis and incremental diagnostic confidence between Baseline visit (T0) and T1 in each arm.
* Changes in the managing physician*s etiologic diagnosis at T3 vs T2 vs T1 in each arm.
* Changes in the managing physician*s diagnostic confidence at T3 vs T2 vs T1 vs T0 in the Early Amyloid PET arm vs the Late Amyloid PET arm.
* The managing physician*s estimate of the likelihood that the patient*s symptoms are due to AD at T3 vs T2 vs T1 vs T0 in the Early Amyloid PET arm vs the Late Amyloid PET arm.
* Changes over calendar time in the placement of amyloid PET imaging in the patient workup for participants in the Free Choice arm.

Patient Management

* The difference between arms (Early Amyloid PET arm, the Late Amyloid PET arm, or the Free Choice arm) in the number of patients randomised to disease-modifying drug (DMD) or any other AD clinical trial at T2.
* The difference between the Early Amyloid PET arm and the Late Amyloid PET arm in number of participants with changes in the management plan (changes in or start of a new program or pharmacologic treatment) at T1 vs T2 vs T3.

Health Economics

* The impact on patient-related outcomes (cognition, anxiety, depression, coping skills, and quality of life) at T3 vs T2 vs T0 in each arm
* The difference in the cost of diagnostic workup to the etiologic diagnosis with very high confidence (*90%) in the Early Amyloid PET arm vs the Late Amyloid PET arm.
* Differences in the use of medical resources (not limited to diagnostic procedures, tests, visits, and hospitalisations) and programs between Early Amyloid PET and Late Amyloid PET arms.
* The number of patients who withdraw from the study.

Imaging Results Assessment

* Descriptive analysis of local visual assessment results
* Mean values of quantitative image assessments (composite cortical standardised uptake value ratios [SUVR] and converted to the centiloid scale) across amyloid PET tracers and by diagnostic subgroup.
* The composite cortical quantitative uptake (SUVR and SUVR converted to the centiloid scale) vs visual reading interpretation
* For each of the amyloid PET tracers, the differences in regional quantitative uptake between diagnostic strata.

For participants in the Early Amyloid PET arm who have a second amyloid PET scan:

* The shift from amyloid positive to amyloid negative, and vice versa.

* The difference in amyloid load, as indicated by quantitative image

assessments, between the first and the second amyloid PET scan

Study description

Background summary

Alzheimer*s disease (AD) is the most common cause of cognitive impairment and dementia and represents over 60% of all dementia cases. The key neuropathological hallmarks of AD include the presence of extracellular deposits of beta-amyloid (A*) peptides, intraneuronal neurofibrillary tangles, and the predominance of neocortical neuronal degeneration. However, despite a clinical assessment, AD is often not recognised, particularly in the early stages or if mixed pathology is present and diagnosis based on clinical criteria alone is difficult. In fact, it is estimated that around 50% of diagnoses in persons presenting with objective cognitive impairment are incorrect. Most commonly, the impairment is attributed to Alzheimer disease. The percentage of incorrect diagnoses is still substantial even in more advanced stages of the disease * comparisons to a neuropathological standard of truth reveal that up to one-third of patients are misdiagnosed. However, beta-amyloid (A*) deposition is considered to be a necessary step on the path toward development of Alzheimer*s disease (AD). Therefore, the depiction of brain A* in vivo can improve an early diagnosis of AD, and, when recognised in a pre-symptomatic population, it might provide an opportunity for secondary prevention of dementia. As a consequence, understanding the value of positron emission tomography (PET) imaging of A* provides a unique opportunity to improve the diagnostic workup of patients suspected to have AD, as well as their management. In addition, the value, timing, and appropriateness of amyloid PET imaging in clinical practice need to be established to allow its cost-effective implementation in the diagnosis process of cognitive decline and dementia.

Study objective

This study (AMYPAD Diagnostic and Patient Management Study) will determine in a real-life clinical setting for whom diagnostic amyloid PET imaging is appropriate, when this is best performed, and how the resulting information is influencing diagnostic confidence, patient management, and ultimately decision trees and cost-effectiveness of dementia care.

Specifically, we will study 3 groups of patients presenting to memory clinics with a cognitive impairment due to AD, specifically those with subjective cognitive decline plus (SCD Plus), mild cognitive impairment (MCI), and

dementia, to determine when amyloid PET imaging helps to exclude AD aetiology (negative predictive value) or conveys an increased risk of AD (positive predictive value) vis-à-vis other information and evidence (clinical, structural imaging, genetic, CSF). Ultimately, the AMYPAD Diagnostic and Patient Management Study will deliver an encompassing diagnostic algorithm allowing a cost-efficient implementation of amyloid PET imaging in the clinical practice. We will study the impact of the information provided by amyloid PET imaging beyond diagnosis by determining the impact on patient management and health resource utilisation, both in the current era of symptomatic treatment and in the context of potentially effective disease-modifying therapies aimed at lowering A* in the brain. Furthermore, we will determine if our diagnostic algorithm is cost-effective from a health care perspective through providing the input of economic modelling, in the context of the current regulatory perspective.

Study design

This is a phase 4 multicentre, open-label study of amyloid PET imaging of participants who have one of the following syndromic diagnoses: SCD-plus, MCI, or dementia where AD is in the differential diagnosis.

The baseline visit must take place within 14 days after the screening visit and can be combined with the screening visit. At baseline, the investigator will record the syndromic diagnosis made by the managing physician, the managing physician*s confidence in that diagnosis, and the managing physician*s estimate of the likelihood that the patient*s symptoms are due to AD. (According to [Johnson et al, 2013], the managing physician is a dementia expert trained and board-certified in neurology, psychiatry, or geriatric medicine who devotes a substantial proportion [at least 25%] of patient contact time to the evaluation and care of adult acquired cognitive impairment or dementia.). The investigator and the managing physician may be but do not have to be the same person.

Participants will be stratified by syndromic diagnosis (SCD-plus, MCI, or dementia) and then randomly assigned (1:1:1) to 1 of 3 arms:
* Early Amyloid PET Arm: Participants will undergo amyloid PET imaging within 4 weeks after the baseline visit. The PET imaging must be performed before any other diagnostic workup, and the results of the scan must be communicated to the managing physician as soon as available and before the managing physician receives the results of any other diagnostic workup. Early Amyloid PET arm participants canl undergo a second amyloid PET scan at 12-18 months after the initial scan. Amyloid load will be defined on the basis of a combination of visual reading and quantitation. The results of the second amyloid PET scan will not be provided to the managing physician and will not be used for clinical purposes.

* Late Amyloid PET Arm: Participants will undergo amyloid PET imaging at 8 months (±8 weeks) after baseline.

* Free Choice Arm: The managing physician will decide whether the participant undergoes amyloid PET imaging. The imaging can be done at any time within 12 months after baseline.

The visits and timepoints are defined as follows: T0 = baseline, T1 = 12 weeks after T0, T2 = 6 months (±14 days) afterT0, T 3 = 13 months (±4 weeks) afterT0, T4 = *28 days after the second PET scan, which will be done 12-18 months after T0 zal (all visits and timepoints are relative to the baseline visit).
T3 and T4 are optional (if applicable).

Intervention

The intervention in this study consists of the addition of amyloid PET scanning to the diagnostic process. Amyloid PET imaging will be conducted at the local sites and read visually, and will not be considered a separate clinical visit.

The study will comprise the following clinical visits and timepoints:
* A baseline clinical visit (Visit 0 [V0] at Time 0 [T0]), within 14 days after screening
* A timepoint 12 weeks after baseline (T1); no clinic visit is required at that time
* A clinical visit at 6 months ±14 days (V1 or T2), and
* A clinical visit at 13 months ±4 weeks (V2 or T3)

At T1, the investigator will review the result communicated by the managing physician (if the investigator and the managing physician are not the same person) and record the etiologic diagnosis made by the managing physician, rate the managing physician*s diagnostic confidence (0% to 100%, visual analogue scale [VAS]) as well as the managing physician*s estimate of the likelihood that the patient*s symptoms are due to AD (0% to 100%, VAS), and record the effective date of the managing physician*s etiologic diagnosis and management plan. This does not need to be a clinical visit.

At the baseline visit, all participants will receive a diary/questionnaire to collect information on the use of medical resources.

Study burden and risks

Risks associated with participation in this study are related to:
- radiation exposure
- idiosyncratic reaction to the radiotracer injection
- placement of the intra-venous catheter
- discomfort during the PET scan
- incidental findings
- potentially confronting questionnaires related to anxiety and depression feelings

- potential disclosure of amyloid PET results which may result in elevated levels of anxiety and stress

Contacts

Public
University of Geneva

Rue Michel-Servet 1
Genève 1206
CH
Scientific
University of Geneva

Rue Michel-Servet 1
Genève 1206
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* The patient can be of any sex, gender, race, or ethnicity.
* SCD-Plus patients must be 60 to 85 years of age
* Patients with MCI or dementia must be 50 to 85 years of age.
* The patient must have a complaint (reported by the patient or by a caregiver) of cognitive problems that are considered by the managing physician to be possibly due to AD., o The patient must be entering a diagnostic assessment for the cognitive complaint.
o The managing physician must feel that knowledge of amyloid status may

increase diagnostic
confidence or alter diagnosis and management.
o Patients should not have known amyloid status prior to randomization, * The patient must satisfy the diagnostic criteria for one of the following:
o SCD-Plus
o MCI
o Dementia, where AD is in the differential diagnosis, * The patient has undergone a dementia blood workup or will have one before amyloid PET.
* The patient has an MRI and/or CT scan or will undergo one before amyloid PET.
* The patient can complete all clinical visits according to the protocol.
* The patient can tolerate a 20-minute amyloid PET scan.
* The patient provides informed consent for study participation and data source verification. In case the patient is randomized to the Early Amyloid PET arm, a new informed consent should be signed before the second imaging session.
* If the patient has dementia, a study partner is available for the duration of the protocol.

Exclusion criteria

Patient must be excluded if they meet any one of the following criteria:
* The patient has another confirmed condition that can fully account for the cognitive impairment, including but not limited to psychiatric disorders (schizophrenia, mood disorders, bipolar disorder and personality disorders; neuroinflammatory, neuroinfective, or neurodegenerative diseases; multiple sclerosis; genetic disorders; HIV; brain injuries; neurosurgery aftereffects; major depressive episode; schizoaffective disorder; delusional disorder; delirium). Patients with long-known, stabilized psychiatric or other brain conditions that cannot fully account for the cognitive impairment may be included in the study
* The patient comes to observation for reasons other than diagnosis (disability assessment for social aids, cognitive assessment for driving license, etc.)
* The patient had a previous A* imaging scan and/or has had other AD biomarker workup
(fluorodeoxyglucose [FDG]-PET and/or cerebrospinal fluid [CSF] analysis) prior to screening. In some centres, the patient may receive a diagnostic workup before screening. These patients can be enrolled if the investigator is blind to the results until after randomization.
* The patient has a life-threatening or unstable medical disease, or a psychiatric condition that could lead to difficulty in complying with the protocol.
* The patient is currently receiving an investigational pharmaceutical product or has participated in a
clinical trial with an investigational pharmaceutical product within 30 days prior to screening, and/or was administered a radiopharmaceutical within 10 radioactive half-lives prior to study drug administration in this study.

* The patient is a woman who is pregnant, planning to become pregnant, or lactating. Pregnancy status of a woman with childbearing potential will be carried out before the PET scan. A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile (www.hma.eu/ctfg.html, Recommendations related to contraception and pregnancy testing in clinical trials, September 2014).
* The patient is employed at the research department or memory clinic, is directly involved with the study, or is a family relative from any department personnel (i.e. partner, older child, sibling, biological or legal representative).
* Any of the contraindications as registered for the study drug used is applicable to the subject. Any of the warnings or precautions as registered for the IMP used is applicable to the subject, unless a risk-benefit assessment is favorable as per the judgement of the sponsor.

Study design

Design

Study phase:	4
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Health services research

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-07-2018
Enrollment:	112
Type:	Actual

Medical products/devices used

Generic name:	Optina Diagnostics Metabolic Hyperspectral Retinal Camera (MHRC)
Registration:	No
Product type:	Medicine

Brand name:	Neuraceq
Generic name:	Florbetaben [18F]
Product type:	Medicine
Brand name:	Vizamyl
Generic name:	Flutemetamol [18F]

Ethics review

Approved WMO Date:	20-03-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-05-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-05-2020
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-002527-21-NL
CCMO	NL64423.029.17