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Are anti-dementia drugs useful in advanced dementia?

Submission date
19/02/2019

Recruitment status
No longer recruiting

Registration date
13/03/2019

Overall study status
Completed

Last Edited
21/08/2019

Condition category
Mental and Behavioural Disorders

[ ] Prospectively registered
[X] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol
Background and study aims
Findings from observational studies and clinical trials have shown the benefits of cholinesterase inhibitors (ChI) with or without memantine for the treatment of mild-to-moderate Alzheimer's disease. However, it is not known whether treatment benefits continue after the progression to severe disease. Therefore, the aim of this study is to evaluate the effect and safety of continuing treatment with ChI with or without memantine in patients with severe dementia.

Who can participate?
302 community-dwelling patients who had been previously treated with ChI (with or without memantine) for at least 3 months and who had severe Alzheimer's disease with or without vascular dementia

What does the study involve?
Participants are randomly allocated to either continue or stop drug treatment, and are assessed after 1, 3, 6 and 12 months (study end).

What are the possible benefits and risks of participating?
This study will provide a scientific basis for better practice guidelines in the treatment of this kind of pathology. This study will provide more evidence on deprescribing and the feasibility of the withdrawal of these drugs in patients with advanced dementia.

Where is the study run from?
GAP Mallorca - unitat d'investigació (Spain)

When is the study starting and how long is it expected to run for?
January 2017 to June 2021

Who is funding the study?
Ministry of Economy and Competitiveness, Carlos III Institute (grant PI16/00720). Support was also provided by the Health Promotion and Preventive Activities-Primary Health Care Network, sustained by a Ministry of Health ISCIII-RETIC award (RD12/0005/0011) and co-financed with European Union ERDF funds.

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Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2017-000042-22

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
PI16/00720

Study information

Scientific Title
Continuation versus discontinuation of treatment for severe dementia: randomized, pragmatic, open-label, clinical trial to evaluate the efficacy of continuing drug treatment in patients with severe dementia

Acronym
STOP-DEM

Study objectives
Even if there is considerable uncertainty on the benefits and harms of both prescribing and deprescribing ChEI, there are guidelines suggesting that deprescription can be proposed according to the references and experiences of the person with dementia and/or their carer /family. Most guidelines recommend individualized discontinuation decisions, but there is essentially no agreement about what findings or situations would warrant discontinuation, or even about what domains to consider in this process. The only relevant domains identified by most authors are a lack of response or a loss of effectiveness, both of which can be difficult to

ascertain in the course of a progressive condition. Well-designed, long-term studies of discontinuation have not been conducted; such evidence is needed to provide a scientific basis for practice guidelines.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Comité d'Ética de la Investigació de les llles Balears (CEl-lB), C/deJesus1s,38A 07010 Palma llles Balears
Tel: 971 17 73 78, Email: ceic_ib@caib.es, 22/02/2017, ref: PI16/720

Study design
Clinical pragmatic multicenter open trial with blinded assessors and a parallel randomized design

Primary study design
Interventional

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Advanced dementia

Interventions
Randomization
A sequence of random numbers will be generated using the Epidat 3.1 program, and used for allocation to each of the two arms. After verification of patient eligibility, the recruiting researchers will make a telephone call to the research unit of the Primary Care Management to determine the group assignment. This allocation will occur after identification of the patient through an algorithm that assigns each patient to the control or intervention group using stratified block randomization. The two groups will be matched for mean durations of treatment with drugs for dementia prior to study onset (6 to 12 months vs. more than 12 months) and age (younger than 74 vs. 75 years or more). The randomization process will be recorded by collecting data from the code request date, patient identification code, and assigned treatment arm. The investigator who approves patient eligibility and requests the randomization will be different from the one who makes evaluations at the study visits. The main and secondary objectives of the study will be evaluated by health professionals who are not on the research team and who will remain blinded to group allocation. The person performing the statistical analysis will also be blinded to group allocation.

Sample size
The total sample size for the primary objective, with a statistical power of 80%, an alpha error of 5%, and a 1:1 ratio of subjects in the two groups, is 251 patients. The assumptions for this calculation are: (i) the incidence of the main outcome measure (time to institutionalization and /or progression of the disability, defined as a loss of 2 of 4 basic functions, or 6 of 11 instrumental functions on the BADLS) is 25% at 12 months; (ii) the minimum HR for detection of a significant difference is 2.09; and (iii) the correlation between the studied variables is 0.002. Based on an assumed loss rate of 20% per year, at least 302 patients will be enrolled.

Recruitment
Potential participants will be identified from the billing records of the Pharmacy of the Health Service of the Balearic Islands and the Neurology Service of the Hospital Son Espases from the previous year. After study onset, the list will be updated every 3 months to identify new candidates. Primary care health centers will be provided with a list of patients receiving treatment with drugs for dementia, and the recruitment will be based on review of their clinical histories. Billing information for 2015 in the Balearic Islands indicated there were 4169 patients over 75 years old who received treatment with a drug for dementia for 3 months or more. The trialists anticipate that they may experience some difficulties in the recruitment due to the fact that the general practitioners participating in this study would be expected to discontinue a drug that was initially prescribed in the hospital setting, mostly by neurologists.

Intervention
Participants will be randomized to continuation or cessation of pharmacological treatment. This intervention will not require phased withdrawal, or any additional follow-up to assure patient safety. Patients will receive the study treatment for 12 months.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Drugs for dementia (a Cholinesterase inhibitor (ChEI) and/or memantine)

Primary outcome(s)
Time to institutionalization and/or progression of disability (defined as a loss of 2 of 4 basic functions, or 6 of 11 instrumental functions using the Bristol activities of daily living scale (BADLS)). Data on the time to institutionalization will be collected by interview with the caregiver and/or review of the clinical history.

Key secondary outcome(s))
1. Cognitive assessment with SMMSE at baseline, 1, 3, 6 and 12 months (study end)
2. Functional assessment with BADLS at baseline, 1, 3, 6 and 12 months (study end)
3. Functional assessment with Functional Assessment (FAST) scale at baseline and 12 months (study end)
4. Advanced dementia quality of life assessed with Quality of Life in Late-Stage Dementia (QUALID) at baseline, 1, 3, 6 and 12 months (study end)
5. Quality of life related to health assessed with EuroQol five dimension (EQ-5D) scale at baseline and 12 months (study end)
6. Psychological and behavioral symptoms associated with dementia assessed with Neuropsychiatric Inventory-Questionnaire (NPI-Q) at baseline, 1, 3, 6 and 12 months (study end)
7. Caregiver overload assessed with Zarit Scale at baseline, 1, 3, 6 and 12 months (study end)
8. Clinical improvement impression assessed with Clinical Global Impression of Change (CGIC) at 12 months (study end)
9. Use of health resources in dementia assessed with Resource Utilization in Dementia (RUD) Lite scale at 12 months (study end)
10. Safety, adverse effects and mortality assessed with adverse effects forms at 1, 3, 6 and 12 months (study end)

Completion date
01/06/2021

Eligibility

Key inclusion criteria
Potential participants will be identified from the billing records of the Pharmacy of the Health Service of the Balearic Islands and the Neurology Service of the Hospital Son Espases from the previous year. After study onset, the list will be updated every 3 months to identify new candidates. Primary care health centers will be provided with a list of patients receiving treatment with drugs for dementia, and the recruitment will be based on review of their clinical histories. Billing information for 2015 in the Balearic Islands indicated there were 4169 patients over 75 years-old who received treatment with a drug for dementia for 3 months or more. We anticipate we may experience some difficulties in the recruitment due to the fact that the general practitioners participating in this study would be expected to discontinue a drug that was initially prescribed in the hospital setting, mostly by neurologists.

This study will include patients with advanced dementia who are living in the community and receiving treatment in a primary care setting or a hospital. Participants must have the following criteria for enrollment:
1. Patient with dementia due to AD, according to National Institute on Aging and Alzheimer's Association (NIA-AA) criteria, with or without small vessel subcortical vascular disease Fazekas 1 or 2
2. Advanced dementia (MMSE ≤ 10)
3. Use of C in stable dose for 6 months or more
4. Completion of informed consent agreement by the caregiver (and the patient when appropriate)
5. Patients without clinical changes of dementia or acute decompensation of concomitant systemic diseases and stable in their pharmacological treatment for dementia or other diseases in the last 3 months

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
1. Patients with non-AD suspected pathology as the main cause of the dementia
2. Life expectancy less than the follow-up duration of the study
3. On a waiting list for interventions or treatments that require hospitalization
4. Participating in another clinical trial

Date of first enrolment

24/10/2018

Date of final enrolment
01/06/2020

Locations

Countries of recruitment
Spain

Study participating centre
GAP Mallorca - unitat d'investigació
C/ Escola Graduada 3
Palma
Spain
07002

Sponsor information

Organisation
Gerencia de Atención Primaria of Mallorca

ROR
https://ror.org/00d9y8h06

Funder(s)

Funder type
Government

Funder Name
Ministry of Economy and Competitiveness, Carlos III Institute (grant PI16/00720)

Funder Name
Support was also provided by the Health Promotion and Preventive Activities-Primary Health Care Network, sustained by a Ministry of Health ISCIII-RETIC award (RD12/0005/0011) and co-financed with European Union ERDF funds

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	11/04/2019	21/08/2019	Yes	No
Participant information sheet		01/11/2016	13/03/2019	No	Yes
Protocol file		03/05/2017	13/03/2019	No	No