



PROTOCOL

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Observational multicentre prospective study to assess changes in cognitive function in patients treated with PCSK9i. Study protocol

Estudio observacional, multicéntrico y prospectivo para evaluar los cambios en la función cognitiva en pacientes tratados con iPCSK9. Protocolo de estudio

José Seijas-Amigo¹, Diego Rodríguez-Penas¹, Ana Estany-Gestal², Pedro Suárez-Artime³, María Santamaría-Cadavid⁴, José Ramón González-Juanatey¹

¹Servicio de Cardiología, Complejo Hospitalario Universitario de Santiago de Compostela (A Coruña). Spain. ²FIDIS-Unidad de Epidemiología e Investigación Clínica, Santiago de Compostela (A Coruña). Spain. ³Servicio de Farmacia, Complejo Hospitalario Universitario de Santiago de Compostela (A Coruña). Spain. ⁴Servicio de Neurología, Complejo Hospitalario Universitario de Santiago de Compostela (A Coruña). Spain.

Author of correspondence

José Seijas Amigo
Hospital Clínico Universitario de Santiago de Compostela. Servicio de Cardiología.
C/ Travesía da Choupana s/n.
15706 Santiago de Compostela (A Coruña), Spain.

Email:
jose.seijas.amigo@sergas.es

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Abstract

Objective: PCSK9 inhibitors have been shown to reduce LDLc by up to about 60% and 85% when used with high doses of statins and ezetimibe (2019 ESC/EAS Guidelines). These therapies may lead to very low levels of LDLc and have been associated with possible cognitive deterioration. No significant differences were found in the only specific study (EBBINGHAUS).

The objective is to prospectively evaluate cognitive deterioration and its repercussion on quality of life and changes in LDLc in patients starting treatment with PCSK9 inhibitors.

Method: It is a postauthorization, multicentre, non-randomized, prospective study. Patients starting treatment for the first time with PCSK9 inhibitors will be recruited in 11 Galician Hospitals over a period of 12 months and with 24 months of follow-up. The primary outcome will be to evaluate changes in cognitive function using the Montreal Cognitive Assessment (MOCA) questionnaire. The secondary outcome will be to evaluate changes in quality of life using the EuroQol-5D. Changes in LDLc will be assessed. The sample size will be 275 patients, taking into account a loss to follow-up of no more than 10%.

Resumen

Objetivo: Los inhibidores de proproteína convertasa subtilisina/kexina de tipo 9 (PCSK9) han demostrado reducir hasta un 60% el colesterol transportado por lipoproteínas de baja densidad (c-LDL) y hasta el 85% asociado a estatinas de alta intensidad y ezetimibe (2019 ESC/EAS Guidelines). Estas terapias pueden dar lugar a muy bajos niveles de c-LDL y se ha especulado sobre su posible relación con deterioro cognitivo. En el único estudio específico, EBBINGHAUS, no se encontraron diferencias significativas.

El objetivo es evaluar prospectivamente el deterioro cognitivo y la repercusión en términos de calidad de vida y variaciones de c-LDL en pacientes que inician tratamiento con inhibidores de PCSK9.

Método: Se trata de un estudio postautorización, multicéntrico, no aleatorizado de seguimiento prospectivo. Se reclutarán pacientes que inicien tratamiento por primera vez con iPCSK9 en 11 hospitales gallegos durante un periodo de 12 meses y un seguimiento de 24 meses. El *endpoint* primario será evaluar los cambios en la función cognitiva a través del cuestionario Montreal Cognitive Assessment (MOCA), y como *endpoints* secundarios se valorarán cambios en la calidad de vida a través del EuroQol-5D y variación de los niveles de LDL. El tamaño muestral, teniendo en cuenta un porcentaje de pérdidas no superior al 10%, será de 275 individuos.

KEYWORDS

Alirocumab; Evolocumab; PCSK9 inhibitors; Cholesterol; Cognition; Lipid-lowering therapies; Safety.

PALABRAS CLAVE

Alirocumab; Evolocumab; inhibidores de la PCSK9; Colesterol; Cognición; Terapias hipolipemiantes; Seguridad.



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The primary outcome will be studied through the dichotomous variable cognitive deterioration (0/1). Cognitive changes over the follow-up period will be analysed using the McNemar test. In addition, an analytical approach using logistic regression will be followed to identify patients at risk of cognitive deterioration. As a result, this analysis will obtain a frequency measurement: the odds ratio (OR). The specific objectives will be studied using bivariate analysis. Continuous contrast variables will be studied using the *t*-test or ANOVA and categorical variables will be studied using the chi-square test.

Conclusions: The MEMOGAL study will provide information on safety in terms of cognitive deterioration in patients starting treatment with PCSK9 inhibitors.

Introduction

Hypercholesterolemia, and increased levels of low-density lipoprotein cholesterol (LDLc) in particular, is a major risk for the development of atherosclerosis and coronary heart disease (CHD), which is the leading cause of death and disability in the Western world.

LDLc has been identified as the main target of cholesterol-lowering therapy and has been accepted as a valid surrogate outcome. Numerous studies have shown that the risk of CHD is decreased by reducing LDLc levels, which is mainly achieved by the use of 3-hydroxy-3-methylglutaryl CoA-reductase (HMG CoA) inhibitors (i.e. statins) and, more recently, the use of PCSK9 inhibitors (PCSK9i). These studies found a strong direct relationship between LDLc levels and CHD events: for every 1 mmol/L (~40 mg/dL) reduction in LDLc, cardiovascular disease (CVD) mortality and morbidity were reduced by 22%. A recent meta-analysis of 81,700 patients showed that PCSK9i reduced the incidence of myocardial infarction by 19% and stroke by 25%².

PCSK9 belongs to the subtilisin serine protease family and is primarily expressed in the liver. PCSK9 plays a key role in the regulation of low-density lipoprotein receptor proteins. Once secreted into plasma, PCSK9 directly binds to the LDLc receptor and stimulates lysosome breakdown after internalisation. The increased degradation of the LDLc receptor results in lower reductions of LDLc, and thus, higher levels of circulating LDLc.

The ODYSSEY³ and FOURIER⁴ clinical trials of 2 PCSK9i (alirocumab and evolocumab) have shown that they reduce LDLc levels by 47.5% as well as the risk of infarction (OR: 0.49)⁵. For this reason, they have been licensed for the treatment of hypercholesterolemia in patients with heterozygous HF or cardiovascular atherosclerosis needing further reductions of LDLc, despite their receiving the highest doses of statins. The ESC/EAS Clinical Guidelines 2019 have reported a reduction of up to 60% in LDLc and up to 85% associated with high-intensity statin therapy and Ezetimibe⁶.

These therapies can sometimes lead to very low LDLc levels, which may be associated with cognitive deterioration. The FDA issued a report in 2012 encouraging studies in this regard. Post-authorization and observational studies have been conducted on statins and cognitive functioning. However, these studies and metaanalyses found no evidence of an association between high-potency statin use and cognitive deterioration^{7,8}.

Subsequent small trials with PCSK9i (LAPLACE, MENDEL, or OSLER) showed no overall statistically significant differences in cognitive deterioration in patients taking these drugs vs placebo. However, LAPLACE-2 and COMBO-1 found an increase in isolated neurocognitive events⁹. A recent metaanalysis of patients treated with alicumab compared adverse events in patients with LDLc < 25 mg/dL in at least two consecutive lab tests with those with LDLc ≥ 25 mg/dL. No differences were found between the two groups in myopathies, abnormal liver enzyme levels, diabetes, or cognitive deterioration. The only adverse event was an increase in cataracts in patients with LDLc < 25 mg/dL (2.6% vs 0.8%)¹⁰. The recently published EBBINGHAUS study¹⁰, which was conducted in parallel with the FOURIER study with evolocumab, included 1,974 patients with a mean follow-up of 19 months. No statistically significant differences were found¹¹.

El objetivo general se estudiará a través de la variable dicotómica deterioro cognitivo (0/1). El estudio del deterioro cognitivo a lo largo del seguimiento se realizará con el test McNemar. Además, se pretende realizar un planteamiento analítico con una regresión logística que explore si existe algún perfil de paciente con riesgo de sufrir deterioro cognitivo. Este análisis obtendrá como resultado una medida de frecuencia, la *odds ratio* (OR). Los objetivos específicos se estudiarán planteando análisis bivariados. Para las variables de contraste continuas se empleará el test *T* o el ANOVA, si las variables son de naturaleza categórica se aplicará el test de chi cuadrado.

Conclusiones: El estudio MEMOGAL intentará aportar información sobre la seguridad en términos de deterioro cognitivo en pacientes que inicien tratamiento con inhibidores de PCSK9 (*real-world evidence*).

Therefore, there is a need for more results from prospective studies using validated methods on the effect of PCSK9i on cognitive function.

The aim of this study is to prospectively evaluate changes in cognitive function in patients treated with alicumab and evolocumab in Galicia (Spain).

Methods

Objectives

The primary outcome will be to evaluate changes in cognitive function in patients naive to PCSK9i treatment (alirocumab and evolocumab) using the MOCA (Montreal Cognitive Assessment) questionnaire.

The secondary outcomes are as follows:

- To evaluate changes in LDL levels from the time of inclusion to the completion of the study.
- To evaluate changes in quality of life using the Spanish version of the 5-level EuroQol 5D version (EQ-5D-5L) questionnaire. These changes will be associated with changes in cognitive function.
- To evaluate the direct costs related to the treatment and consultations.

Design

Multicentre observational study with prospective follow-up, quasi-experimental epidemiological design, and a nonconcurrent control group.

Population

Patients will be recruited from the following public hospitals in Galicia, Spain: Hospital Clínico Universitario de Santiago, Hospital Universitario de Ourense, Hospital Álvaro Cunqueiro (Vigo), Hospital Provincial de Pontevedra, Hospital Barco de Valdeorras, Hospital Virxe da Xunqueira (Cee), Hospital Arquitecto Macide de Ferrol, Hospital Universitario de A Coruña, Hospital da Costa (Burela), Hospital Universitario Lucus Augusti (Lugo), Hospital del Barbanza and Hospital Comarcal de Monforte.

Eligibility criteria

Inclusion criteria:

- Be at least 18 years old.
- Be able to understand the aims of the study and give informed consent to participate.
- To start with the first funded dose of PCSK9i.

Exclusion criteria:

- Diagnosis of any disease related to cognitive deterioration.

Intervention

In patients diagnosed with homozygous or heterozygous familial hypercholesterolemia and/or patients with cardiovascular disease (ischemic heart disease, ischemic cerebrovascular disease, or peripheral artery disease) who have been prescribed evolocumab or alicumab for the first time, in whom LDLc has not reached < 100 mg/dL after statin treatment at the maximum tolerated dose or presented statin intolerance, and have shown good compliance with statin medication (≥ 80% per dispensing record).

Variables

Main variables

Cognitive deterioration: Yes/No on the MOCA test.

Epidemiological variables

- Gender (M/F).
- Age (years).
- Date of the visit (dd/mm/yyyy).
- Date of birth (due to data protection laws only mm/yyyy can be recorded in the study).
- Familial hypercholesterolemia (Y/N).
- Cardiovascular disease (Y/N).
- Date of diagnosis.
- Family history of dementia.
- Smoker (Y/N/EX-smoker).
- Alcohol consumption (U/week). 1 Unit (1 glass of wine/beer).
- Diet (Y/N).
- Diabetes (Y/N).
- Hypertension (Y/N).
- Heart failure (Y/N).
- COVID-19 (Y/N)^{12,13}:
 - Hospitalized due to COVID-19 (Y/N) - (date).
 - IgG serology (+/-).
- Height (cm).
- Weight (kg).
- BMI.
- Minimum exercise: walking 30 min/d (YES/NO).
- Level of education: (illiterate; compulsory education; high school; university).
- Annual income: (< €20 000; €20 000-35 000€; > €35 000).
- LDL (mg/dL) and Lp(a) levels at a date as close as possible to the visit day and date.
- PCSK9i dispensed:
 - Type (evolocumab/alirocumab).
 - Dose (mg).
- Statin:
 - Type.
 - Dose (mg).
- Baseline evaluation of health status using EQ-5D-5L.

Follow-up variables

- Date of visit (dd/mm/yyyy).
- Levels of LDLc (mg/dL); total cholesterol (mg/dL); non-HDL-cholesterol (mg/dL); and Lp(a).
- Evaluation of health status (EVA) using EQ-5D-5L.
- Social tariff for EQ-5D-5L health states (1.0000 to -0.6533).
- Compliance (%).
- Direct costs (€): Medical consultation (DOG) + price of drugs (Spanish Ministry of Health).

Study procedures

Recruitment stage and pre-prescription visit

Patients will be invited to participate at consultations in the Pharmacy Services of the participating hospitals. Following the first prescription PCSK9i

drugs by a specialist physician, patients will go to the pharmacy as part of routine clinical practice for the dispensing of prescriptions.

The assignment of a patient to a particular therapeutic strategy will not be decided in advance in the study protocol. Assignment will be determined according to standard medical practice, and the decision to prescribe a particular drug would be clearly dissociated from the decision to include the patient in the study. No intervention, either diagnostic or follow-up, other than standard clinical practice will be applied to patients, and epidemiological methods will be used to analyse the data collected.

Follow-up

Patients will be followed up within a window of ± 2 months at the visits listed below. Follow-up visits will coincide with the drug dispensing visits at the pharmacy.

Sample size and recruitment

An estimated 250 individuals could be included in the study, according to the following aspects: i) the recruitment time proposed by the research team; ii) recruitment taking place in all Galician hospitals; and iii) the number of patients to whom this drug is prescribed per year.

The aim is to obtain an estimate of the percentage of individuals who develop cognitive deterioration as an adverse effect of the drugs under study. A previous study has shown that this percentage is approximately 5% ($p1 = 0.05$). If 250 individuals are included in the study, the accuracy of the estimation would be $\pm 2.70\%$ ($w = 0.27$) using a two-tailed ($c = 2$) asymptotic normal 95% confidence interval ($\gamma = 0.95$).

In addition, the rate of treatment compliance is expected to be high, given that candidate patients must have a profile of compliance with medication: thus, the estimated percentage lost to follow-up should be no more than 10%. This means that the final number of participants should be 275.

Sample size was calculated using Ene 3.0 statistical software.

Data source

Medical records: The clinical history of each patient will be accessed to collect the clinical data needed to achieve the proposed objectives.

Questionnaires

At each scheduled visit, the following validated questionnaires will be handed out and must be completed by each participant:

- MOCA test.
- Barthel test.
- EQ-5D-5L test.

Data management

The data registry will be managed using a database specifically designed for this purpose. Data will be coded and each participating centre will create their own anonymisation code. The information recorded by each participating centre will be transferred to the study sponsor and principal investigator in a pseudonymised manner.

Statistical analysis

Descriptive and bivariate analysis

Categorical variables will be expressed as frequencies and percentages and continuous variables will be expressed as means and standard

Table 1. Flowchart

	Inclusion	6-month visit	12-month visit	18-month visit	Final visit (24 months)
Informed consent	X				
MOCA	X		X		X
EQ-5D	X		X		X
Barthel Index	X				X
LDL levels (laboratory test)	X	X	X	X	X

deviations or medians and interquartile ranges. Goodness of fit will be determined using Lilliefors test, which is based on the Kolmogorov-Smirnov test.

Primary outcome analysis

The primary outcome will be analysed via the dichotomous variable cognitive deterioration (0/1). We will analyse whether there are differences in the contrast variables of interest and the tests of choice will depend on the type of these variables.

Cognitive deterioration during follow-up will be analysed using the McNemar test for paired data.

In addition, patient profiles at risk of experiencing cognitive deterioration will be determined using logistic regression. This analysis will provide the odds ratio (OR) as a frequency measure with 95% confidence intervals.

Secondary outcomes analysis

The secondary outcomes will be studied using bivariate analyses. The grouping variables will be categorical. Continuous contrast variables will be studied using the *t*-test or ANOVA (or their corresponding nonparametric tests in the case of a nonnormal fit), and categorical variables will be studied using the chi-square test.

Ethical and legal aspects

The protocol was approved by the Drug Research Ethics Committee of Galicia. The clinical trial project will be developed in full compliance with the World Medical Association's 1964 Declaration of Helsinki and subsequent ratifications (Tokyo 75, Venice 83, Hong Kong 89, West Somerset 96, Scotland 00, Seoul 08, and Fortaleza 13) on ethical principles for medical research on human beings, with Spanish Royal Decree 1090/2015 issued on 24th December on clinical trials, specifically the provisions of article 38 about good clinical practice, and with the European Convention on Human Rights and Biomedicine issued on April 4, 1997 in Oviedo, Spain.

The researchers participating in this study undertake that all clinical data collected from the participants will be processed to guarantee data anonymity such that they cannot be traced to personal identifiable data in compliance with the General Data Protection Regulation (EU) 2016/679 of the European Parliament and the European Council of April 27, 2016. Data collection and processing will also be in full compliance with the following Spanish regulations: Law 3/2018 on the Protection of Personal Data and guarantee of digital rights; Law 41/2002 of November 14 (which regulates patient autonomy and rights and obligations regarding clinical information and documentation); Law 3/2001 of May 28 (regulating informed consent and the clinical history of patients); Law 3/2005 of March 7, amending Law 3/2001; and Decree 29/2009 of February 5 regulating access to electronic clinical histories.

It shall be ensured that the decision to prescribe the medicinal product (alirocumab/evolocumab) is clearly dissociated from the decision to include the patient in the study. Patient enrolment will always be subsequent to and independent of the prescribing process.

The patients' clinical data will be collected by the investigator in the study-specific Data Collection Book (DCB). Each DCB will be pseudonymised to protect the identity of the patient. Only the research team and the health authorities, who are under oath of confidentiality, will

have access to all the data collected for the study. Only nonidentifiable information may be passed on to third parties. Once the study has been completed, the data will be anonymised for future use by requesting express permission to do so from the participants in the informed consent form.

Data processing, communication, and transfer will be conducted in accordance with the provisions of the General Data Protection Regulation (Regulation (EU) 2016/679 of the European Parliament and Council of April 27, 2016) and the Organic Law 3/2018 of December 5 on the Protection of Personal Data and Guarantee of Digital Rights. The centre where the information is obtained is the data processor.

Commitment to publish

The results obtained in the design of this project will be presented at conferences and in scientific journals addressing this area of knowledge, regardless of whether or not they are the results expected or proposed by the researcher.

Discussion

This research project will generate a multicentre database of patients treated with PCSK9i in the last 2 to 3 years in Galicia, Spain (Real-World Evidence).

These data will provide results on the use of PCSK9i and possible cognitive deterioration caused by very low levels of LDLc.

The strengths of the study are its prospective design and an approach aimed at detecting neurocognitive changes through specific questionnaires such as the MOCA test.

Its limitations include the number of patients recruited and the follow-up period, which is a consequence of the observational prospective study design. We concluded that the strength of this study would be superior to a retrospective cohort study with its known limitations.

We will also obtain results on lipid control in the Galician population at high cardiovascular risk and the relationship between LDLc levels and real-life cardiovascular events. These results will help to outline the current situation and determine whether the objectives of previous clinical trials are being achieved.

Values of Lp(a) (as well as ApoA1 and ApoB) and their relationship with the composite endpoint of major adverse cardiac events (MACE) (i.e. cardiovascular death, nonfatal stroke and nonfatal myocardial infarction) will be obtained as well as the incidence of MACE events due to high levels of both LDLc and of Lp(a). Results will be obtained on the use of PCSK9i to reduce Lp(a). We will also obtain results about the use of these drugs for this therapeutic target which, to date, lacks pharmacological treatments.

Results will be obtained on quality of life that will be used in future pharmacoeconomic analyses.

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Conflict of interest

No conflict of interests.

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