ABSTRACT

- **Title**

RETrospective Observational Study of Evolocumab Use in Spanish Endocrinology Units (RETOSS-Endo)

- **Keywords**

Hyperlipidemia, familial hypercholesterolemia, diabetes, evolocumab, endocrinology

- **Rationale and Background**

Type 2 diabetes mellitus (DM) is a major independent risk factor for coronary heart disease (CHD) and stroke, and concomitant dyslipidemia aggravates the cardiovascular (CV) risk (1). In Spain, Hospital Endocrinology Units are responsible for the clinical care of patients with hypercholesterolemia, with special attention to two types of patients with high/very high CV risk profiles: atherogenic hyperlipidemia associated with DM and familial hypercholesterolemia (FH).

Evolocumab (Repatha®) is a fully human monoclonal immunoglobulin G type 2 (IgG2) antibody directed against proprotein convertase subtilisin/kexin type 9 (PCSK9) which increases liver low density lipoprotein receptor (LDLR) levels resulting in associated reductions in serum low density lipoprotein-cholesterol (LDL-C). In Spain, evolocumab is reimbursed by the Spanish National Health System since 20th January 2016.

Data from recent studies in the Spanish population show that, among diabetic patients with dyslipidemia and FH patients, there is a high proportion of patients that continue to experience high plasma LDL-C levels despite current medical care and treatment approaches (2,3). The present systematic, serial chart review study aimed to describe the clinical characteristics and management in the first weeks of patients initiating evolocumab in Real World Life in Hospital Endocrinology Units in Spain. At present there is no information describing evolocumab use in real-world setting.

- **Research Question and Objectives**
  - Primary Objective:
    - To describe the main clinical characteristics (LDL-C levels, DM status, FH status prior to treatment initiation) of patients with hyperlipidemia initiating evolocumab in Hospital Endocrinology Units.
  - Secondary Objective:
    - To describe other clinical characteristics of patients with hyperlipidemia initiating evolocumab in Hospital Endocrinology Units.
    - To describe the clinical management of patients initiating evolocumab treatment in Hospital Endocrinology Units.
  - Exploratory Objective:
    - To describe the referral process of patients initiating evolocumab treatment in Hospital Endocrinology Units.
  - Hypothesis:
    - No formal hypothesis was tested in this observational study.
- **Study Design:** Retrospective, observational, serial chart review
- **Setting**

At the individual patient level, data was captured for up to 24 weeks (up to 12 weeks pre-initiation evolocumab and 12 weeks post-initiation of evolocumab).

At the study level, data was captured for the periods spanning 13 March 2018 and 18 September 2018.

A total of 21 sites in Spain participated in the study. Sites and principal investigators are listed in Section 3.

- **Patients and Study Size, Including Dropouts**
  - Patient Eligibility Criteria:
    - Inclusion Criteria:
      - Adults (≥18 years) at the time of evolocumab initiation.
      - Provided informed consent if applicable according to local requirements.
      - Initiated on evolocumab at physician's discretion, independent of study protocol, from February 1st 2016 to April 30th 2017, by an specialist in a Hospital Endocrinology Unit in Spain.
      - Received at least one dose of evolocumab at physician's discretion, by an specialist in a Hospital Endocrinology Unit in Spain.
      - At least one LDL-C measurement within the 12 weeks prior to initiation of evolocumab (last value available in the previous 12 weeks).
    - Exclusion Criteria:
      - Enrolled in a study with a PCSK9 inhibitor within 12 weeks prior to initiation of evolocumab.
      - Received a PCSK9 inhibitor within 12 weeks prior to initiation of evolocumab.
      - Enrolled in a clinical study during the retrospective observational period i.e. 12 weeks pre-initiation of evolocumab or up to 12 weeks after evolocumab initiation.
  - Study Sample Size:

    The primary outcome measures for the study involved estimating the percentage of patients with clinical characteristics of interest (FH, DM) and also estimating the baseline LDL-C levels. The planned sample size for the study was 150 patients.

    The sample size was expected to enable precise estimates of the outcome measures to be obtained.

- **Variables and Data Sources**
  - <u>Primary Outcome Measures</u>
    - Clinical characteristics at baseline comprising:

- LDL-C pre-initiation of evolocumab (last value available in the previous 12 weeks).
- DM status at evolocumab initiation (diagnosed/not diagnosed, year of diagnosis).
- FH status at evolocumab initiation (diagnosed/not diagnosed, year of diagnosis).

- Secondary Outcome Measures
  - Demographic and clinical variables at evolocumab initiation (age, race, gender, employment status, waist circumference, systolic blood pressure, diastolic blood pressure, heart rate, height, weight).
  - Family medical history (only first-degree relatives) at evolocumab initiation.
  - Medical history at evolocumab initiation.
  - Cardiovascular (CV) history at evolocumab initiation.
  - Laboratory parameters over time.
  - Clinical factor/s that determined evolocumab prescription at initiation.
  - Use of evolocumab and other lipid-lowering therapies (LLTs) over time.
  - Statin Intolerance (Yes/No).
  - Foreseen frequency of routine visits after the first 12 weeks of evolocumab treatment.
- Exploratory Outcome Measures
  - Specialty of the physician that referred the patient to the Hospital Endocrinology Unit for initiating evolocumab treatment (if apply) and main reason for patient referral.
  - Number of visits and type of other specialties consulted by the patients in the Hospital during the 24 weeks retrospective follow-up period.
  - Hospital where evolocumab was initiated.
  - Specialty of the physician that first diagnosed hypercholesterolemia.

- **Results**

A total of 120 patients were included in the study, with a 92.5% of patients presenting FH (this includes both patients with FH and patients with familial combined hyperlipidemia), being 72.5% heterozygous FH and 3.3% homozygous FH. At baseline the mean (standard deviation [SD]) time since FH diagnosis was 12.6 (12.5) years, with 33.0% of patients being diagnosed for over 10 years.

A 25.0% of patients presented DM (23.3% DM Type 2). The mean (SD) time since DM diagnosis was 9.8 (8.4) years, with 36.7% of patients having been diagnosed for >10 years. A 35.8% of patients were statin intolerant. Up to 55.0% of patients presented a prior CV event, with a 44.2% of patients with FH and without prior CV event.

The mean age (SD) was 57.0 (11.5) years old, and 51.7% of the population were female.

A 75.8% of patients aged ≤65 years and 62.5% were treated with ezetimibe during second-line treatment. The most frequent body mass index (BMI) classification was obesity grade 3-4 in 34.2% of patients.

At baseline, a total of 56.7% of patients had a family history of CV events. Regarding patients' medical histories, at baseline a total of 5.8% of patients presented heart failure, 8.3% stroke (100% ischemic), 2.5% TIA, 25.8% carotid artery disease, and 12.5% peripheral artery disease. A 25.0% of patients had had angina (73.3% stable) and 21.7% myocardial infarction (50.0% of which were STEMI [ST-segment elevation myocardial infarction]; 15.4% missing). A 30.0% of patients presented coronary artery bypass.

Prior to evolocumab initiation, the mean (SD) LDL-C level was 180.2 (62.2) mg/dL, with 33.3% of patients having ≥130 and <160 mg/mL, 21.7% of patients ≥160 and <190 mg/mL and 33.3% of patients ≥190 mg/mL, whereas 5% of patients had <100 mg/dL. After 8 weeks of initiating evolocumab, the mean (SD) LDL-C level was 83.0 (63.8) mg/dL, with a mean absolute change from baseline of -91.7 (56.5) mg/dL, and a mean relative change of -54.3 (31.8; 95% CI: -62.8 to -45.8) %. The percentage of patients achieving LDL-C levels <100 ml/dL after 8 weeks of evolocumab initiation was 70.2%, with 56.1% reaching <70 mg/dL, 33.3% reaching <50 mg/dL, and 10.5% reaching <30 mg/dL.

In the post-hoc analysis of the last observed LDL-C levels, there was a total of 107 patients with available data. After a mean (SD) of 8.8 (3.2) weeks of evolocumab treatment, the mean (SD) LDL-C level was 94.0 (66.3) mg/dL, with a mean absolute change of -83.4 (65.9) mg/dL, and a mean relative change of -45.0 (54.3; 95% CI: -55.4 to -34.6) %.

At evolocumab initiation, the most commonly administered LLT was oral ezetimibe (50% of patients; mean dose 10 mg, once daily), followed by oral high-intensity statins (46.7%). A 22.6% of patients receiving ezetimibe at evolocumab initiation discontinued ezetimibe over the first 12 weeks after evolocumab initiation.

A 35.8% of patients presented statin intolerance, mainly to atorvastatin (74.4% of intolerant patients)

Within the first year of evolocumab treatment and after the first 12 weeks of follow-up, the mean (SD) number of routine visits was of 1.8 (0.99), with a minimum of 0 and a maximum of 5.

A total of 25 (20.8%) of patients were referred to the Hospital Endocrinology Unit for initiating evolocumab treatment, mainly from another Unit within the same hospital (72.0% of referred patients). The most frequent specialty from which the patient was referred was primary care physician in 8 patients (32.0%). The main reason for patient referral was hyperlipidemia control (N=10; 40.0%).

A total of 52 (43.3%) patients consulted other medical specialties during the 12 weeks prior to evolocumab initiation. Among these patients, 21 (40.4%) visited their cardiologist (mean [SD] visits: 1.2 [0.5]).

The percentage of patients consulting other medical specialties during the 2 weeks after evolocumab initiation was of 54.5% (N missing= 109). After 4 weeks, the percentage was of 31.3% (N missing= 104); after 8 weeks it was 28.3% (N missing= 74); and after 12 weeks it was 31.9% (N missing= 73). In all studied time points the most frequently visited specialist was the cardiologist.

Mainly, the hypercholesterolemia was diagnosed by an endocrinologist (47.5%), followed by a primary care physician (19.2%) and by an internist (11.7%).

- **Conclusion**

In Spanish Hospital Endocrinology Units, evolocumab was predominantly prescribed in patients with FH and/or atherosclerotic cardiovascular disease. Evolocumab use was aligned with 2016 ESC/EAS PCSK9 inhibitor guidelines, but with higher baseline LDL-C levels than the recommended thresholds, possibly because evolocumab was administered in patients with no further therapeutic alternatives. LDL–C levels were significantly reduced after evolocumab treatment.

- **Marketing Authorization Holder(s):** Amgen Europe B.V.

Names and Affiliations of Principal Investigators

Name	Site Name	Department
[redacted]	Hospital Universitari Son Espases	Servicio de Endocrinologia y Reumatologia
	Hospital Can Misses	Servicio de Endocrinologia
	Hospital General Universitario de Alicante	Servicio Endocrinologia y Nutricion
	Hospital Universitario San Juan de Alicante	Servicio Endocrinologia
	Hospital Universitario Ramon y Cajal	Servicio de Endocrinologia
	Hospital Montecelo	Servicio de Endocrinologia
	Hospital Clinic i Provincial de Barcelona	Servicio de Endocrinologia y Nutricion
	Hospital Universitari Parc Tauli	Servicio de Endocrinologia y Nutricion
	Hospital de Fuerteventura	Servicio de Endocrinologia
	Hospital Universitario Insular de Gran Canaria	Endocrinologia
	Hospital Universitario de Burgos	Servicio de Endocrinologia y Nutricion
	Hospital Regional Universitario de Malaga	Servicio de Endocrinologia y Nutricion
	Hospital Universitario Virgen de la Victoria	Servicio de Endocrinologia
	Hospital Universitario Central de Asturias	Servicio de Endocrinologia
	Hospital Universitario de Alava	Servicio de Endocrinologia

[redacted]	Hospital de Galdakao	Servicio de Endocrinologia
	Hospital Clinico Universitario de Valencia	Servicio de Endocrinologia
	Hospital General Universitario Gregorio Marañon	Servicio de Endocrinologia y Nutricion
	Hospital Virgen de La Salud	Departamento de Endocrinologia
	Hospital Vital Alvarez Buylla de Mieres	Servicio de Medicina Interna
	Hospital Virgen del Puerto	Servicio de Endocrinologia