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SCIENTIFIC LETTER

First clinical and efficacy data on evolocumab in routine clinical practice in endocrinology and nutrition services in Spain: A retrospective observational study (RETOSS-ENDO)

Primeros datos clínicos y de eficacia de evolocumab en práctica clínica habitual en servicios de endocrinología y nutrición en España: un estudio observacional retrospectivo (RETOSS-ENDO)

Endocrinology and nutrition departments are among the departments that care for patients with high or very high cardiovascular risk, such as patients with diabetes mellitus (DM) and patients with familial hypercholesterolaemia (FH). DM is an independent risk factor for atherosclerotic cardiovascular disease.[1] One of the main causative factors in these diseases is low-density lipoprotein cholesterol (LDL-C).[2] On this point, controlled studies have provided robust scientific evidence on the importance of reducing LDL-C to decrease cardiovascular risk.[3]

The development and clinical availability of PCSK9 inhibitors have represented a breakthrough in the management of hypercholesterolaemia, as they help patients with high or very high vascular risk achieve the treatment goals recommended by the guidelines of various scientific associations.[4,5] The FOURIER study found that evolocumab reduced LDL-C levels by more than 60% and also significantly reduced the number of cardiovascular events in patients with prior atherosclerotic cardiovascular, cardiac, cerebral or peripheral disease over a period of 2.2 years.[6] The reduction was similar in patients with or without T2DM, but the absolute risk of reductions was higher in patients with T2DM.[7] In addition, the ODYSSEY OUTCOMES study with alirocumab found a reduction in the relative risk of cardiovascular events in patients with recent coronary syndrome.[8]

The objective of this study was to report the clinical characteristics (LDL-C levels and history of DM and/or FH), demographic characteristics and changes over time in lipid levels (including total cholesterol, LDL-C, high-density lipoprotein cholesterol [HDL-C], triglycerides and non-HDL cholesterol) of the first patients to be treated with evolocumab in clinical practice in endocrinology and nutrition departments in Spain.

A multicentre, retrospective, observational study was designed with a consecutive review of all medical records for patients who were seen. Patients who started treatment with evolocumab in 21 endocrinology and nutrition departments (between February 2016 and April 2017) in Spain, as per routine clinical practice, who met the screening criteria (patients $\geq$18 years, with at least one dose of evolocumab in the above-mentioned period and with an LDL-C test) were included. The latest laboratory parameters within the 12 weeks prior to starting treatment with evolocumab were considered baseline values and clinical data were collected up to 12 ± 4 weeks after starting evolocumab.

The study protocol was approved by the ethics committees and all the patients signed the informed consent form. A descriptive statistical analysis was performed for all the variables.

A total of 120 patients were included with a mean age of 57.0 years (standard deviation [SD] 11.5); 51.7% were women and 88.3% had FH (72.5% heterozygous FH). In total, 55.0% had at least one prior cardiovascular event, primarily coronary revascularisation (54.5%), carotid atherosclerotic disease (47.0%), angina (45.5%), myocardial infarction (39.4%), peripheral arterial disease (22.7%) or ischaemic stroke (15.2%), and 25.0% had DM (23.3% T2DM). The mean baseline LDL-C level was 180.2 mg/dl (SD 62.2). After eight weeks of treatment, the mean LDL-C level fell to 83.0 mg/dl (SD 63.8), representing a 54.3% reduction from baseline (95% CI: 62.8%, 45.8%), and 33.3% achieved levels <50 mg/dl. Fig. 1 shows changes over time in the different lipid parameters at eight weeks. In patients with DM, the baseline mean LDL-C level was 176.9 mg/dl (SD 79.4), with a 74.0% reduction, which enabled 66.7% of patients to achieve LDL-C levels <50 mg/dl.

As they were the first patients to receive this therapy, it is not surprising that their baseline LDL-C level was unusually high (180 mg/dl). However, despite such high starting levels, the patients achieved significant LDL-C reductions (−54.3%; 95% CI: −62.8%, −45.8%) after just eight weeks of treatment with evolocumab, which were greater in the subgroup with T2DM (−74.9%).

According to the new treatment goals set out in the recent guidelines, 83% of patients with DM would be under the target set for high-risk patients (<70 mg/dl) and 67% would be under the new target set for very high-risk patients (<55 mg/dl) after treatment with evolocumab. The results of this study were obtained in a population that did not achieve the treatment goals and could not be offered an alternative treatment. This was reflected in the fact that 36% of the patients were intolerant to statins, 50% were treated with ezetimibe, 47% were treated with high-intensity statins and 5.8% were treated with moderate-intensity statins.

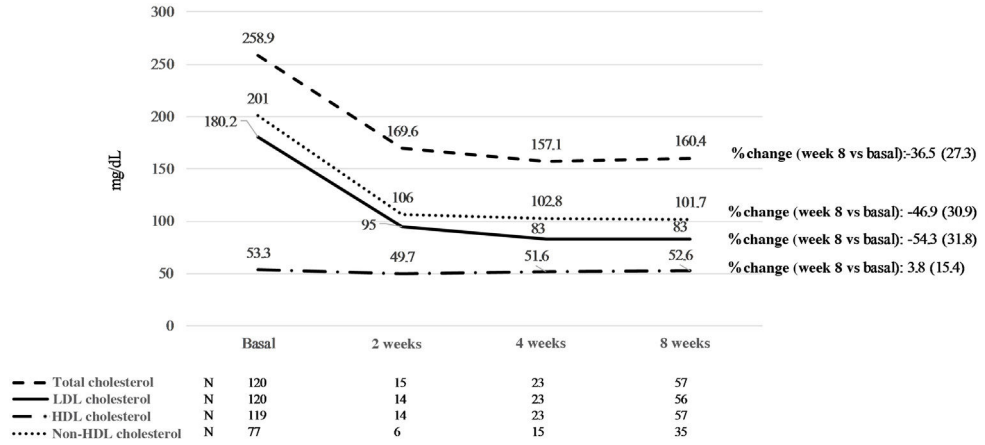

Figure 1 Changes over time in total cholesterol, LDL cholesterol, HDL cholesterol and non-HDL cholesterol levels during treatment with evolocumab.

It is important to highlight the high rate of short-term treatment adherence (98.2%), with a 96.7% rate of self-administration; just six patients stopped treatment with evolocumab.

The study had some limitations inherent to its design, with a limited observation period. It also had a small sample size, which limited evaluation by subgroups.

This first study of evolocumab in routine clinical practice in endocrinology and nutrition departments confirmed the results obtained in both randomised clinical trials and other routine clinical practice studies.[9,10]

In conclusion, it was seen that, in endocrinology and nutrition departments, the first patients prioritised for treatment with evolocumab under routine clinical practice conditions were patients with FH who, in more than half of cases, had already experienced one or more prior vascular events. Of the patients included, 23% had T2DM. In this initial phase of availability of the therapy, the use of evolocumab was adjusted to the established regimens for the use of inhibitors, but with initial LDL-C levels significantly higher than the recommended thresholds, perhaps because evolocumab was administered in patients with no other treatment options. Despite this, and consistent with the results of prior clinical trials, LDL-C levels fell significantly (54% compared to baseline and 74% in the subgroup of patients with DM) very quickly: eight weeks after starting treatment with evolocumab.

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Antonio Pérez Pérez[a,*],
Emilio Ortega Martínez de Victoria[b],
Francisco Arrieta Blanco[c], Assumpta Caixàs Pedragós[d],
Estefanía Santos Mazo[e], Pablo Fernandez-Catalina[f],
Sergio Martínez-Hervas[g], José Antonio López-Medina[h],
Lorena Suárez-Gutiérrez[i], Juan Ramón Urgeles Planelles[j],
Sònia Gatell Menchén[k], Francisco Tinahones Madueño[h]

[a] *Servicio de Endocrinología y Nutrición, Hospital de Sant Pau, Barcelona, Spain*
[b] *Servicio de Endocrinología y Nutrición, Hospital Clinic i Provincial de Barcelona, Spain*
[c] *Servicio de Endocrinología y Nutrición, Hospital Universitario Ramón y Cajal, Madrid, Spain*
[d] *Servicio de Endocrinología y Nutrición, Hospital Universitari Parc Taulí, Sabadell, Spain*
[e] *Servicio de Endocrinología y Nutrición, Hospital Universitario de Burgos, Spain*
[f] *Servicio de Endocrinología y Nutrición, Hospital Montecelo, Pontevedra, Spain*
[g] *Servicio de Endocrinología y Nutrición, Hospital Clinico Universitario, Valencia, Spain*
[h] *Servicio de Endocrinología y Nutrición, Hospital Universitario Virgen de la Victoria, Málaga, Spain*
[i] *Servicio de Endocrinología y Nutrición, Hospital Universitario Central de Asturias, Oviedo, Spain*
[j] *Servicio de Endocrinología y Nutrición, Hospital Universitari Son Espases, Palma de Mallorca, Spain*
[k] *Departamento Médico, Departamento Médico, Amgen, S.A., Spain*

[*] Corresponding author.
E-mail address: aperez@santpau.cat (A. Pérez Pérez).

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Likely impact of COVID-19 on referrals to pediatric endocrinology: Increased incidence of precocious puberty in a third-level hospital

Probable impacto de la COVID-19 sobre las derivaciones a endocrinología infantil: aumento de incidencia de pubertad precoz en un hospital de tercer nivel

The first case of coronavirus disease 2019 (COVID-19) was detected in Wuhan (China) in December 2019; from then, it started to spread throughout the world. Confirmed cases and deaths shot up rapidly,[1] taking an emotional toll on the population, with symptoms of anxiety, stress and depression.[2]

In Spain, schools shut down between 9 March and 13 March 2020. On 14 March, a state of alarm was declared, and on 16 March, the population was put in lockdown. On 5 April 2020, 130,759 cases of COVID-19 had been recorded in Spain, 1,200,000 cases had been confirmed worldwide and more than 68,000 people had died.[1] Spain became the country with the third largest number of people affected by this pandemic in the world.

For many citizens, this was their first social and healthcare emergency, caused by a viral agent, giving rise to a great deal of uncertainty and adverse health consequences.[1]

The pandemic might have prompted a change in the type and number of referrals to different specialisations; therefore, we set out to determine whether there was a decrease or delay in referrals to paediatric endocrinology at a tertiary hospital, as well as their distribution. To this was added a subjective impression among paediatric endocrinology staff of an increase in the number of referrals for precocious puberty, which made it necessary to confirm whether the pandemic was influencing the time of onset of puberty, as a third objective.

We conducted a retrospective case–control study with non-probability consecutive sampling of children under 14 years of age first referred from primary and specialised care to the paediatric endocrinology department of a tertiary hospital between March 2019 and December 2019 or March 2020 to December 2020, recorded in the consultation software program.

Data were collected on all primary and secondary diagnoses from the first visit, as well as the month of referral.

The criteria used for patient selection were:

- Inclusion criteria: children under 14 years of age first referred to the paediatric endocrinology department at our hospital during an 18-month period.
- Exclusion criteria: age over 14 years, false first visits and duplicate referrals for a single patient.

Statistical analysis consisting of comparison of independent means was carried out using R software. The inferential test of normality using the Shapiro–Wilk test was applied in advance.

In 2019, there were a total of 598 referrals to the paediatric endocrinology department meeting the established criteria (control group), whereas in 2020, there were a total of 471 referrals in the same time period.

The most common reasons for referral during the control period were: short stature 37.5% (224/598), obesity 17.4% (104/598) and hypothyroidism 15.4% (92/598); the most common reasons for referral in the 2020 case group were: short stature 27.8% (131/471), precocious puberty 18.5% (87/471) and hypothyroidism 14% (66/471) (Fig. 1).

Given that these were normal samples, the differences between all the reasons for referral were analysed using Student's t test, yielding statistical significance for short stature ($p = 0.0019$), obesity ($p = 0.0002$), precocious puberty ($p = 0.0092$) and bone mineral density abnormalities ($p = 0.0328$).

A homogeneous distribution in referrals in 2019 was seen, with a decrease during the holiday months, whereas in 2020 there was a predominance of referrals in the final three months of the year.

Lockdowns, school closures and the need for social distancing led to less exercise, less healthy eating and longer periods of time at home and in front of screens.[3] In addition, anxiety and financial concerns among parents, along with fears of becoming ill, might have caused stress in children.[4]