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Research Paper

Monoclonal Antibodies for Treatment of Hyperlipidemia: A Real World Data Analysis in the Three Years after Introduction Into Clinical Practice

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ABSTRACT
In the last few years therapeutic options for treatment of hypercholesterolemia has been enriched with a new class of drugs: PCSK9 inhibitors (PCSK9i) (8). These are biological drugs, monoclonal antibodies capable of inhibiting the PCSK9 protein, which plays a central role in the metabolic fate of the LDL receptor, resulting in a reduction in the circulating levels of this lipoprotein. In order to estimate the use of PCSK-9i in the Calabria region, a retrospective study was conducted from July 2017 to December 2019 in Calabria Region (Italy). The reports of adverse reactions occurring in patients treated during the study period were extrapolated from Regional Pharmacovigilance Network. Subsequently they were evaluated through the Naranjo algorithm. In study period were dispensed 10885 units and €2346780,00 costs incurred. Trends from 2017 to 2019 are growing, reflecting both the increase in patients receiving PCSK9i and the increase in expenditure incurred by the Regional Health Service. Only 3 suspected adverse reactions related to PCSK9i were reported in Regional Pharmacovigilance Network. Analysis with Naranjo's algorithm reveals that they are all non-serious. The intrinsic value of this study consists in photographing, albeit partially, the current governance capacity of the Regional Health System in South of Italy. PCSK-9i represent the therapeutic innovation with the greatest impact in terms of cost, indications, and therapeutic efficacy.

KEY WORDS:
PCSK9 inhibitors (PCSK9i)
Evolocumab
Alirocumab
Adverse Drug Event (ADR)
Naranjo's algorithm

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I. BACKGROUND

Hyperlipidaemias are the main risk factor for the first manifestations of atherosclerosis and consequent complications, such as acute myocardial infarction, cerebral stroke and peripheral vasculopathy (1). Today statins represent the first-choice therapeutic treatment for the reduction of blood levels of low-density lipoprotein cholesterol (LDL-C) (2-3). However, only one in four high-risk patients, who have taken statins for at least 3 months, are able to lower their LDL cholesterol level below 70 mg / dL (4). Real-world data suggests that most patients start treatment with medium-strength statins that reduce LDL-C levels by about 30% (5-6). In recent years, a protein called proprotein convertase subtilisin/kexin 9 (PCSK9), which plays a central role in the metabolic fate of the LDL receptor, has been identified and studied (7).

To date, therefore, the range of therapeutic options for the treatment of hypercholesterolemia has been enriched with a new class of drugs: PCSK9 inhibitors (PCSK9i) (8). These are biological drugs, monoclonal antibodies capable of inhibiting the PCSK9 protein, which plays a central role in the metabolic fate of the LDL receptor, resulting in a reduction in the circulating levels of this lipoprotein (8). Recent studies have shown that PCSK-9, in addition to regulating plasma levels of LDL (LDL-C) by modulating hepatic expression of the LDL

receptor (LDL-R), plays a key role in processes independent of receptor activity, including the metabolism of triglyceride-rich lipoproteins (TRLs) in the intestine and liver and the regulation of lipoprotein levels (Lp(a)) (9). PCSK-9i binds to the PCSK-9 protein preventing it from interacting with the LDL-R complex and avoiding the intracellular degradation of the receptor itself and promotes its recycling on the surface of the hepatocytes with consequent reduction of the circulating levels of LDL-C (10).

The first marketing authorization of PCSK9i granted in Europe by the European Medicines Agency (EMA) is dated for the evolocumab in June 2015 (11). In Italy the formal possibility to prescribe of both evolocumab and alirocumab was completed with the activation of the specific register of drugs monitored on the portal of the Italian Medicines Agency (AIFA) in 2017. The reimbursement and use of these drugs have been regulated by AIFA Determines 172/2017 (12) and 256/2017 (13).

They provide that the following categories of patients can be treated under the reimbursement scheme with these drugs:

- patients with heterozygous familial hypercholesterolemia (FH) (homozygous only evolocumab) resistant to conventional therapy (with or without a history of cardiovascular disease);
- patients with non-FH hypercholesterolemia or mixed dyslipidaemia with a history of vascular disease and resistant to conventional therapy;
- patients with FH and non-FH hypercholesterolemia resistant to conventional therapy because they are intolerant to statins;
- patients with complicated diabetes mellitus and arterial hypertension.

Resistant hypercholesterolemia means the persistence of LDL-C values> 100 mg / dl in secondary prevention or> 130 mg / dl in primary prevention (FH only), despite the presence of therapy with high potency / efficacy statins (atorvastatin> 40 mg / day, rosuvastatin> 20 mg / day) associated with ezetimibe. These values must be confirmed in 3 controls after at least 2 months (total 6 months of follow-up) (8).

The objective of the study is to determine the direct healthcare costs in the period 2017-2019, related to drug therapy in patients treated in the Calabria Region with PCSK-9i; as well as observe the incidence of adverse events of PCSK-9i drugs reported in Regional Pharmacovigilance Network.

II. MATERIAL AND METHODS

In order to estimate the use of PCSK-9i in the Calabria region, a retrospective study was conducted on two different administrative databases in order to identify all the subjects who from July 2017 to December 2019 had received a prescription of PCSK9i (evolocumab or alirocumab) as well as the units dispensed. The expenditure incurred for the purchase of drug therapies was instead calculated by considering the ex-factory price net of SSN discounts. The reports of adverse reactions occurring in patients treated during the study period were extrapolated from the regional spontaneous reporting database of adverse events (Regional Pharmacovigilance Network, RPN). Subsequently, the same were subsequently evaluated through the Naranjo algorithm (14). The most popular algorithms are Naranjo's and WHO's. The spontaneous reporting system in Italy uses the Naranjo algorithm for drug reporting.

III. RESULTS

The data from the OsMed 2018 Report show that nationally in 2017, 2,608 patients were initiated for treatment with PCSK-9i in the treatment of hypercholesterolemia, of which 1,516 with evolocumab and 1,092 with alirocumab. 66.4% of the prescriptions were addressed to male subjects while the remaining 33.6% to female subjects. The median age of the subjects enrolled in the registers is 61 years (range 18-80) (15). The 2018 OsMed Report shows that in the Calabria Region, in the same year 2017, a total of 96 patients were initiated for treatment, respectively 73 with evolocumab and 23 with alirocumab (15).

The data extrapolated from the regional administrative databases made it possible to evaluate the units dispensed and the expenditure incurred in the years 2017, 2018 and 2019 (table 1) for every Local Health System (LHS). Trends from 2017 to 2019 are growing, reflecting both the increase in patients receiving PCSK9i and the increase in expenditure incurred by the Regional Health Service.

In 2018, several clinical trials of the PCSK-9i were concluded: AMG145-20110118, FOURIER and AMG145-20140316.

The dispensed dosage units consisted to a greater extent of evolocumab from 2018, with a percentage increase of + 163.70%. Most of the patients using PCSK9i belong to the ASP of LHS 1, as can be seen from the data present in Table 2.

From the consultation of the reports for suspected adverse reactions (ADRs) present in the regional database, the regional pharmacovigilance network (RPN) analysed the reporting forms for suspected adverse reactions related to PCSK9i and subsequently 3 reporting forms were processed. The average age of the patients for whom the ADR form has been completed is 65.33 years and 75% of them are male. One of these ADRs was

attributable to alirocumab while the other 2 to evolocumab. In all cases, patients had been taking the therapy for about 45 days. The analysis of the characteristics of the ADRs highlighted are shown in Table 3.

IV. DISCUSSION

From the analysed usage and expenditure data, it appears that in the three-year period 2017-2018, there was a greater use of evolocumab compared to alirocumab. It would appear that clinicians have prescribed evolocumab to a greater extent, although comparative efficacy and safety studies between the two molecules have not yet been published, and literature data suggest that the two molecules have a similar efficacy and safety profile. However, the incidence of use still remains too low compared to the potential uses in the resident population. In fact, previous studies have revealed that the potential real users in the Calabria Region were 637 (16).

The analysis of the evolocumab and alirocumab packs dispensed in the region would suggest that doctors have confidence in the new treatments but the progressive increase in the number of patients treated has occurred too slowly especially considering that treatment with PCSK9i reduces the absolute risk of subjects with LDL- C> 100 mg / dl of approximately 1% per year (17), as can be seen from the literature data (18) (19).

The main limitation of the study is represented by the fact that it was conducted on administrative databases and from which it was possible to extrapolate only prescription and expense data, not contemplating the clinical outcomes of the treatments. In fact, it is proposed to carry out therapy adherence studies in order to monitor the course of the disease as well as the achievement of the therapeutic target, since as for the other lipid-lowering agents, also for PCSK-9i it is essential to maintain a continuous treatment to achieve the goal of C-LDL.

The efficacy of treatment with monoclonal antibodies with PCSK-9i on the incidence of cardiovascular events, both fatal and non-fatal, must be constantly considered in real-life and cannot be considered exclusively on the data of available clinical trials. The reporting of adverse events in patients treated with newly introduced drugs allows to evaluate not only the efficacy but above all the safety of drugs in a real care setting in poly-treated and unselected patients. Post-marketing surveillance studies can represent an important alternative source of data, especially with regard to the detection of a signal relating to new adverse drug reactions (ADRs).

The ADRs that emerged from RPN are non-serious. In particular, a total of 3 interesting ADRs have been reported in table 3. These are 2 common reactions (≥1/100, <1/10) relating to skin and subcutaneous tissue pathologies for both evolocumab and alirocumab, such as itching and reaction at the injection site; and urticaria which is a rare reaction (≥1/10,000, <1/1,000) in the case of evolocumab. The definition of the frequency of adverse reactions was obtained from the technical data sheet study of evolocumab (20) and arilocumab (21). Through the Naranjo algorithm, it allowed the assessment of the causal link (causality assessment) between the drug and the adverse event, allowing us to assess that the adverse reaction reported in the reporting form was actually caused by the drug in question.

V. CONCLUSION

Given the poor lipid control and the problems related to the use of statins in patients with high cardiovascular risk, the evaluation of new lipid-lowering drugs becomes relevant not only in terms of efficacy but above all in terms of safety (17).

The intrinsic value of this study consists in photographing, albeit partially, the current governance capacity of the Regional Health System. PCSK-9i represent the therapeutic innovation with the greatest impact in terms of cost, indications, and therapeutic efficacy. For all patients with familial dyslipidaemia who require treatment and do not respond or tolerate statins, PCSK-9i are an essential therapeutic option. It is therefore clear that access to PCSK9i inhibitor drugs is still below the expected level and that the patient's therapeutic pathway management system (eligibility, treatment and follow-up) is still complex and this slows down access. The need to make the path more coordinated is emphasized by focusing on the organizational aspects that guarantee greater prescriptive appropriateness.

Table 1. Dispensed Units and costs incurred in study period

	Units			Costs		
Local Health System	2017	2018	2019	2017	2018	2019
1	309	1.585	3.201	69.617	338.287	677.340
2	55	547	2.298	20.814	114.459	491.422
3	149	648	986	30.820	135.314	206.789
4	56	275	325	15.154	56.775	67.326
5	18	207	226	4.991	58.639	59.033

Total	587	3.262	7.036	141.396	703.474	1.501.910
LHS= Local Health System						

Table 2. Evolocumab and Alirocumab units used in Calabria Region in the period 2017-2019.

	Unità			Spesa		
	2017	**2018**	**2019**	**2017**	**2018**	**2019**
EVOLOCUMAB	365	1.879	4.955	78.754	405.426	1.068.553
LHS 1	267	1.174	2.387	57609,279	253.308,13	514.440,49
LHS 2	0	93	1.651	0,00	20.069,39	356.255,99
LHS 3	64	360	605	13.808,96	77.675,40	130.538,02
LHS 4	22	124	146	4.746,83	26.754,86	31.501,72
LHS 5	12	128	166	2.589,18	27.617,92	35.816,99
ALIROCUMAB	222	1.385	2.095	62.642	298.449	436.158
LHS 1	42	411	826	12008,06	84.978,78	165.301,34
LHS 2	55	454	647	20.813,96	94.390,10	135.166,00
LHS 3	85	290	383	17.011,47	58.039,03	76.651,42
LHS 4	34	151	179	10.406,99	30.020,26	35.824,11
LHS 5	6	79	60	2.401,61	31.020,88	23.215,60
LHS= Local Health System						

Table 3. Characteristics of the ADRs and interpretation of the ADRs through the Naranjo algorithm.

Active Ingredient	**ADR**	**Naranjo's Algorithm**
Alirocumab	Itching	Probable
Evolocumab	Rash	Possible
	Urticaria	Probable

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