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Association between causative mutations and response to PCSK9 inhibitor therapy in subjects with familial hypercholesterolemia: A single center real-world study

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Abstract *Background and aims:* Familial hypercholesterolemia (FH) is an autosomal dominant disease that leads to cardiovascular (CV) disease. Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9-I) demonstrated efficacy in low-density lipoprotein cholesterol (LDL-C) reduction and in prevention of CV events. The aim of our study is to evaluate the relationship between LDL receptor (*LDLR*) mutations and response to PCSK9-I therapy.
Methods and results: We evaluated total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) in consecutive patients with FH before PCSK9-I treatment and after 12 (T12w) and 36 (T36w) weeks of treatment. We evaluated LDL-C target achievement according to different mutations in *LDLR*. Eighty FH subjects (mean age:54 ± 13.3 years), 39 heterozygous (He) with defective *LDLR* gene mutations, 30 He with null mutations and 11 compound-He or homozygous (Ho) were recruited. At baseline, 69 subjects were under maximal lipid lowering therapy (MLLT) and 11 subjects had statin-intolerance. From baseline to T36w we observed an overall 51% reduction in LDL-C. We found no difference in LDL-C changes between subjects with He-defective mutation and He-null mutations both at T12w ($p = 1.00$) and T36w ($p = 0.538$). At T36w, LDL-C target was achieved in 59% of He-defective mutations subjects and in 36% of He-null mutations subgroup ($p = 0.069$), whereas none of compound-He/Ho-FH achieved LDL-C target.
Conclusions: After 36 weeks there were no differences in response to PCSK9-I therapy between different groups of He-FH subjects. Response to PCSK9-I was significantly lower in carriers of compound-He/Ho mutations.
Registration number for clinical trials: NCT04313270 extension.

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Introduction

Strong evidence highlights low-density lipoprotein cholesterol (LDL-C) role as the main causative factor in atherosclerosis development [1]. Familial hypercholesterolemia (FH) is an autosomal dominant disease with a clinical picture represented by high LDL-C levels since childhood and premature cardiovascular (CV) events [2]. FH prevalence is 1:250 for heterozygous-FH (He-FH) and 1:160,000 for homozygous-FH (Ho-FH) [2,3]. The primary genetic FH cause is related to mutations in *LDLR* gene encoding for Low-density Lipoprotein Receptor (LDLR) [4], with mutation in *apolipoprotein B* (*APOB*) and Proprotein convertase subtilisin/kexin type 9 (*PCSK9*) genes being also reported as causative [5]. Both null (loss-of-function) and defective (mainly missense) mutations in *LDLR* gene are reported, with the severity of LDLR impairment being related to degree of receptor activity loss and, in turn, to disease severity of FH [4,6].

Although statin therapy represented for years the gold standard lipid-lowering therapy, LDL-C target is not always achieved [7]. More recently, PCSK9 inhibitors (PCSK9-I) demonstrated efficacy in LDL-C reduction, in the prevention of CV events and subclinical atherosclerosis changes [8–12].

PCSK9 has been recognized for its key role in LDL-C metabolism [13]. The binding of PCSK9 to LDLR promotes receptor degradation, thus reducing LDL particles removal [14]. An analysis of 6 randomized controlled trials (RCTs) from the ODYSSEY program (758 Alirocumab-treated and 433 controls) showed a consistent lipid-lowering effect to Alirocumab in different genotypes of *LDLR*, *APOB* and *PCSK9* [15]. However, clinical trials are designed to test efficacy and safety of novel therapy under ideal circumstances. In contrast, clinical practice is affected by multiple confounding factors such as variable patient adherence, presence of co-morbidities, concomitant treatments. Thus, real-world evidence has been recognized as a way to shed light on a more comprehensive knowledge of treatment effectiveness [16]. Although, several evidence showed the efficacy of PCSK9-I in a real world setting [17–19], at the best of our knowledge no data are currently available on efficacy and safety of PCSK9-I according to *LDLR* mutations. Thus, in the present study, we evaluated the association between *LDLR* mutations and response to PCSK9-I in a real-world setting.

Methods

From July 2016 to August 2020, in the context of LIPIGEN, a national project on familial dyslipidaemia [20], consecutive subjects attending the lipid clinic of the Department of Clinical Medicine and Surgery, Federico II University Hospital with very high levels of LDL-C (above the 95th percentile when compared with a sex- and age-matched general population), with clinical diagnosis of FH (DUTCH Lipid Clinic Network score >8) were screened for inclusion in the present study. The protocol was approved by Federico II University local ethic Committee (approval code 2015/261). The present study is an extension of the study with ClinicalTrials.gov identifier NCT04313270.

The major inclusion criteria were a diagnosis of FH and the eligibility of subjects to start a treatment with PCSK9-I according to Italian Drug Administration Agency (AIFA) criteria for PCSK9-I prescription: LDL-C levels were $\geq$2.59 mmol/L ($\geq$100 mg/dL) with established CVD or $\geq$ 3.35 mmol/L ($\geq$130 mg/dL) and without CV in 3 different determinations despite maximal tolerated lipid lowering therapy (MLLT). Exclusion criteria were: age $<$18 years, inability to understand or sign the informed consent, presence of hypercholesterolemia secondary to other causes (hypothyroidism, hormone therapies, corticosteroids etc.), absence of mutation in *LDLR* gene, previous exposure to PCSK9-I, end-stage renal disease (filtration rate $<$30 ml/min/m^2), high level of transaminases ($>3\times$ upper normal limit), current malignant disease or a diagnosis of malignancy in the 2 years prior to the first visit. Subjects enrolled in the study continued the ongoing lipid lowering therapy and added a PCSK9-I (Alirocumab 150 mg or Alirocumab 75 mg or Evolocumab 140 mg subcutaneous injection every 14 days or Evolocumab 420 mg every 28 days).

Study protocol

After informed consent, a detailed medical history was recorded for each patient. Data about age, gender, previous and/or current medical conditions, current and past lipid lowering treatments, vascular risk factors and previous CV and cerebrovascular events were collected.

Body mass index (BMI) was calculated as body weight/(height^2). Clinical diagnosis of FH was achieved using Dutch Lipid Clinic Network Score and subsequently a genetic testing to assess major causative mutations in the *LDLR* gene was performed [21–23].

The decision to prescribe either alirocumab or evolocumab was independent from study participation, and all treatment decisions remained at the discretion of the treating physician.

Statin intolerance was defined as clinical or laboratory adverse events attributed to the statin therapy according to EAS consensus panel statement [22].

To the best of our knowledge, there are not specific guidelines to define ezetimibe intolerance. However, ezetimibe intolerance was defined as the inability to tolerate the drug according to patient's adverse events (AE) and/or objective parameters (i.e., increased levels of aspartate aminotransferase, or alanine aminotransferase) [24].

Adherence to MLLT was evaluated by physician during subject interview through follow-up visit [25]. A patient was defined non-adherent to treatment when missing one or more PCSK9-I dose administration [26].

Genetic analysis

Genetic analysis was performed by PCR amplification and direct sequencing of the promoter, all exons and respective exon–intron junctions of the *LDLR* gene as previously

described [21,27]. The multiplex ligation-dependent probe amplification (MLPA) was used to search for large rearrangements in the *LDLR* gene [28]. If mutations were not identified, the direct sequencing was extended to PCSK9 gene and to the exons 26 and 29 of APOB gene [28].

Blood laboratory parameters

In all enrolled subjects total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and LDL-C were evaluated at baseline (before starting PCSK9-I), 12 weeks (T12w) and 36 weeks (T36w) after treatment with PCSK9-I. TC, TG, HDL-C measured using standard enzymatic methods, LDL-C was calculated according to the Friedewald formula [29]. According to documentation provided by the US Food and Drug Administration, a clinically meaningful response to PCSK9-I was defined as a reduction in LDL-C of at least 15%.

In addition, we evaluated LDL-C target achievement during treatment with PCSK9-I according to ESC/EAS guidelines [2].

Statistical analysis

Statistical analysis was performed with the IBM SPSS 26 system (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as mean ± standard deviation (SD). The t-test was performed to compare continuous variables for paired samples and for independent samples. In case of values with a skewed non-Gaussian distribution, Mann–Whitney U test was used to compare means. The χ^2 test or Fisher's exact test were used to compare categorical variables. All results were expressed as 2-tailed values, p values < 0.05 being statistically significant.

Primary outcome was represented by the assessment of lipid changes stratifying subjects according to genotype in heterozygous (He) with defective mutations, He with null mutations and subjects with compound He and homozygous (Ho) mutations.

In addition, given the potential influence of clinical characteristics and population heterogeneity we performed sub-group analyses to assess changes in lipid profile and LDL-C target achievement at T12w and at T36w stratifying according to mutations in *LDLR* gene and background MLLT (statin + ezetimibe, ezetimibe alone, statin alone).

Results

As reported in Supplemental Fig. 1, a total of 130 patients were screened for inclusion. Fifty were excluded because of the presence of exclusion criteria. Eighty subjects (44 males and 36 females, mean age 54.0 ± 13.3 years) with FH confirmed by molecular testing were enrolled. All patients carried mutations in the *LDLR* gene: 39 He-FH with defective mutations in *LDLR* gene (missense or small in frame deletions), 30 He-FH with null mutations (splicing, large deletions, deletion leading to frameshift and nonsense variants) and 11 compound-He/Ho-FH subjects.

At the time of eligibility assessment to receive a PCSK9-I treatment, according to AIFA criteria, 66 (83%) subjects were receiving high-intensity statin treatment [30] (28 atorvastatin 40 mg, 1 atorvastatin 80 mg, 25 rosuvastatin 20 mg, 12 rosuvastatin 40 mg), 3 (2%) subjects were receiving moderate-intensity statin treatment [30] (1 was under simvastatin 40 mg, 1 atorvastatin 20 mg, 1 rosuvastatin 10 mg). Ezetimibe was present as co-treatment in 69 (86%) subjects and as monotherapy in 11 (14%) subjects with documented statin-intolerance. At T12w, no changes were made on statin therapy. However, 7 (9%) subjects discontinued ezetimibe therapy due to a reported intolerance. At T36w, one patient reported total lipid lowering therapy withdrawal and was excluded by the analysis (Table 2).

Previous CV events were reported by 29 subjects (36.6%), with coronary artery disease being reported in 25 cases and ischemic stroke in 4 cases. Major baseline clinical and demographic characteristics of the study population are reported in Table 1, and different mutations found in He-FH patients are reported in Supplemental Table 1. Clinical, demographic and genetic characteristics of compound-He/Ho-FH group are reported in Supplemental Table 2.

Changes in serum lipid profile

As showed in Fig. 1, at T12w subjects reported a significant reduction in levels of TC (from 261 ± 79 to 159 ± 75, $p < 0.001$), LDL-C (from 189 ± 76 to 90 ± 73, $p < 0.001$) and TG (from 116 ± 114 to 96 ± 49 $p = 0.005$), with a trend towards increase in HDL-C (from 48 ± 11 to 50 ± 13, $p = 0.051$). Overall, the mean reduction was 39% for TC and 55% for LDL-C. At T12w, a >15% LDL-C reduction as compared to baseline values was found in 92.5% of subjects, whereas 7.5% of subjects did not achieve a LDL-C reduction >15% (5 Ho-FH and 1 statin intolerant patient). No adverse events related to PCSK9-I were reported and subject compliance to therapy was 100% at T12w.

T36w data were available for 66 subjects because 2 subjects were lost at follow-up, 6 had a shorter observation period, 6 subjects added Evinacumab to MLLT in the frame of an international trial.

Compared with baseline values, at T36w (Fig. 1) subjects reported a significant reduction in levels of TC (from 261 ± 69 to 159 ± 69, $p < 0.001$), LDL-C (from 183 ± 76 to 90 ± 67, $p < 0.001$) and TG (from 116 ± 113 to 94 ± 46 $p = 0.010$) whereas non-significant changes were observed for HDL-C (from 48 ± 11 to 50 ± 11, $p = 0.261$). The mean reduction was 36% for TC and 49% for LDL-C. A >15% LDL-C reduction as compared to baseline values was found in 90.4% of subjects.

A total of 9 (13%) subjects (1 Ho-FH, 4 He-defective, 4 He-null) were not adherent to therapy at T36w assessment. Of these, 4 reported mild adverse events (mild hyper-transaminasemia in 3 subjects and site injection reaction in 1) and 5 lost one or more PCSK9-I administrations.

Table 1 Clinical and demographic features of subjects with familial hypercholesterolemia starting a treatment with PCSK9 inhibitor.

Variable	Study subjects (n = 80)	Defective-He (n = 39)	Null-He (n = 30)	Compound-He/Ho (n = 11)
Age (years)	54 ± 13.3	55.1 ± 13.9	55.3 ± 12.2	44.1 ± 10.4
Male gender, *n* (%)	44 (55%)	21 (54%)	17 (57%)	6 (55%)
Hypertension, *n* (%)	48 (60%)	24 (62%)	18 (60%)	6 (55%)
Cardiovascular events, *n* (%)	29 (36%)	13 (33%)	12 (40%)	4 (36%)
Coronary artery disease	25 (31%)	11 (28%)	11 (37%)	3 (27%)
Stroke	4 (5%)	2 (5%)	1 (3%)	1 (10%)
Obesity, *n* (%)	18 (23%)	11 (28%)	4 (13%)	3 (27%)
Diabetes, *n* (%)	4 (5%)	3 (8%)	1 (3%)	0 (0%)
Smoking habit, *n* (%)	18 (23%)	7 (18%)	10 (33%)	1 (10%)
Body Mass Index (BMI) (kg/m^2)	27 ± 4	27 ± 5	27 ± 3	26 ± 4
Systolic Blood Pressure (mmHg)	125 ± 13	125 ± 11	124 ± 14	127 ± 18
Diastolic Blood Pressure (mmHg)	76 ± 9	77 ± 8	75 ± 10	74 ± 9
DUTCH score	18.5 ± 4	16.9 ± 2.7	17.9 ± 3	25.7 ± 4
Carotid Intima Media Thickness, *n* (%)	24 (30%)	9 (23%)	14 (46%)	1 (10%)
Carotid Plaque, *n* (%)	39 (49%)	18 (46%)	13 (43%)	8 (73%)
Total Cholesterol (mg/dl)	261 ± 79	247 ± 61	259 ± 83	316 ± 108
Triglycerides (mg/dl)	98 (IQR: 69–127)	104 (IQR: 83–144)	92 (IQR: 63–119)	90 (IQR: 62–109)
HDL-C (mg/dl)	48 ± 11	49 ± 9	50 ± 14	41 ± 7
LDL-C (mg/dl)	189 ± 76	170 ± 57	189 ± 76	258 ± 101
Statin intolerance	11 (14%)	7 (18%)	4 (13%)	0 (0%)

Note. Data are presented as mean ± standard deviation for continuous variables with a normal distribution and median (interquartile range IQR) for non-parametric continuous variables.

Fig. 2 reports percent (%) changes in lipid profile from baseline to T12w and T36w according to *LDLR* gene mutations. We found no differences in LDL-C % changes between subjects with He-defective mutation and He-null both at T12w ($p = 1.00$) and T36w ($p = 0.538$). In contrast, in compound-He/Ho-FH group we observed a less significant % reduction in LDL-C as compared to overall He-FH group ($p < 0.001$) at T12w and at Tw36 ($p = 0.006$).

In Table 2 are shown % changes in LDL-C at T12w and T36w stratified according to *LDLR* gene mutations and concomitant lipid lowering therapy. Statin + Ezetimibe treatment was used by ~75% of He-FH subjects and in 90–100% of compound-He/Ho-FH. Among Statin + Ezetimibe treated patients, a similar reduction in LDL-C was observed in He-null and He-defective at T12w (57% vs 65%, $p = 0.072$) and at T36w (51% vs 60%, $p = 0.221$). Patients receiving statin alone or ezetimibe alone with PCSK9-I had a LDL-C reduction >55%, both in He-null and He-defective FH.

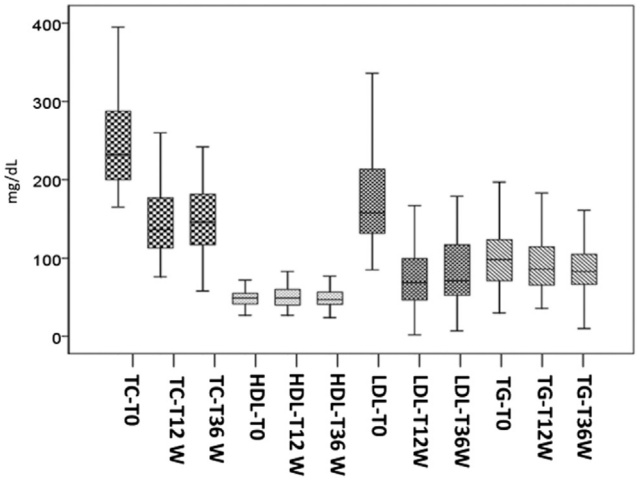

Figure 1 Overall changes in lipid profile from baseline to T12w and to T36w Abbreviations: TC total cholesterol; **LDL** low-density lipoprotein; **HDL** high-density lipoprotein; **TG** triglycerides; **T0** baseline; **T12**w Time 12 weeks; **T36**w Time 36 weeks.

LDL-C target achievement

LDL-C target achievement, defined according to ESC/EAS guidelines [2], was obtained in 34 out of 80 subjects (43%) at T12w and in 30 out of 68 subjects (44%) at T36w.

In Fig. 3 is showed percentage of target achievement at T12w and at T36w stratifying according to *LDLR* gene mutations. We found no difference between He-null and He-defective subgroups in the rate of LDL-C target achievement at T12w ($p = 0.916$) and at T36w ($p = 0.069$), whereas none of subjects with compound-He/Ho-FH achieved LDL-C target.

Discussion

In the present study we evaluated, for the first time in a real-world setting, response to PCSK9-I in a group of FH subjects according to different types of causative mutations (presence of defective or null mutations in *LDLR* gene).

We included in our study 39 He-FH with defective mutation, 30 He-FH with null mutation in *LDLR* gene and 11 compound-He/Ho-FH subjects. Notably, the number of subjects with He-defective mutation is similar to the number of subjects with He-null mutation making all comparisons methodologically reliable.

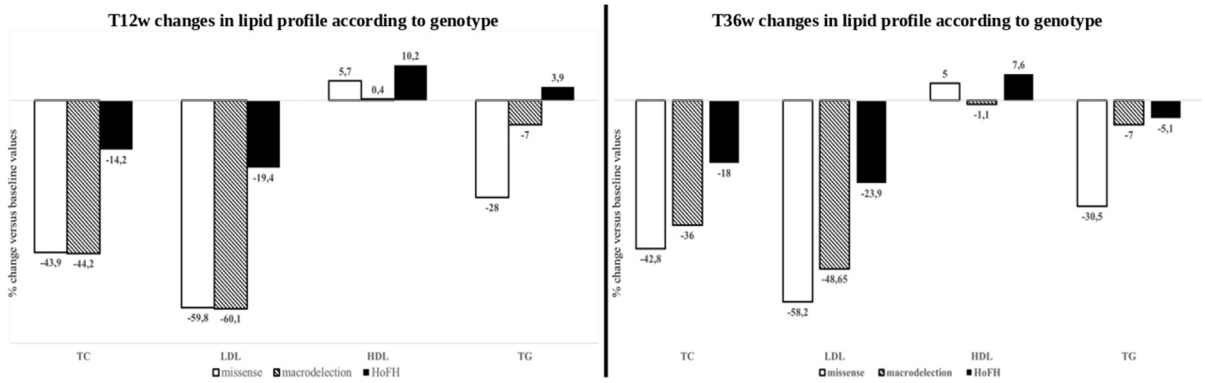

Figure 2 **Percent changes in lipid profile according to genotype from baseline to T12w (left panel) and at T36w (right panel). Abbreviations:** **TC** total cholesterol; **LDL** low-density lipoprotein; **HDL** high-density lipoprotein; **TG** triglycerides; **T12**w Time 12 weeks; **T36**w Time 36 weeks; **HoFH** homozygous familial hypercholesterolemia.

After 12 and 36 weeks of treatment with PCSK9-I, ≈ 90% of subjects showed a reduction of LDL-C levels >15%, with a mean overall LDL-C reduction >50%. These results are in line with data from RCTs on PCSK9-I efficacy and safety [8,9].

Stratifying study population according to *LDLR* gene mutation, we found no differences in changes in lipid profile at T12w and T36w between He-defective subgroup and He-null subgroup. Our results confirm and extend data from an analysis of 6 RCTs from the ODYSSEY program showing that there were no significant differences in LDL-C changes between He-defective and He-null subgroup during treatment with Alirocumab [15].

In contrast, we observed a significantly lower LDL-C reduction in compound-He/Ho-FH subgroup (≈20%) as compared to He-FH (≈50%). This finding is supported by data from TESLA and TAUSSIG clinical trials showing that Evolocumab induces a ≈25% LDL-C reduction in Ho-FH subjects on top of MLLT [31]. It is well established that in Ho-FH and compound-He subjects the LDL-R expression and function are deeply impaired [32]. Moreover, a recent study demonstrated that residual LDLR function and expression are the main determinants of LDL clearance in Ho-FH subjects [33]. These pathophysiological mechanisms could explain the less effective PCSK9-I mediated LDLR up-regulation observed in compound-He/Ho-FH as compared to He-FH subjects [33].

Furthermore, we performed an analysis to investigate a potential influence of background lipid lowering therapy on PCSK9-I efficacy according to different underlying *LDLR* gene mutation. We found that >90% of compound-He/Ho-FH subjects were receiving statin + ezetimibe. Thus, in this subgroup, the limited lipid-lowering efficacy of PCSK9-I

Table 2 Percent change in low-density lipoprotein cholesterol (LDL-C) during treatment with PCSK9 inhibitor according to genotype and concomitant lipid lowering therapy at T12w (left) and T36w (right).

T12w			T36w		
Genotype (%)	MLLT (%)	LDL-C %	Genotype	MLLT (%)	LDL-C %
He-defective N = 39	Statin + Ezetimibe (n = 29)	−65%	He-defective N = 33	Statin + Ezetimibe (n = 24)	−60%
	Ezetimibe alone (n = 7)	−45%		Ezetimibe alone (n = 7)	−47%
	Statin alone (n = 3)	−58%		Statin alone (n = 2)	−69%
He-null N = 30	Statin + Ezetimibe (n = 23)	−57%	He-null N = 27[a]	Statin + Ezetimibe (n = 20)[a]	−51%[a]
	Ezetimibe alone (n = 4)	−71%		Ezetimibe alone (n = 4)	−61%
	Statin alone (n = 3)	−58%		Statin alone (n = 3)	−61%
compound-He/Ho N = 11	Statin + Ezetimibe (n = 10)	−23%	compound-He/Ho N = 6	Statin + Ezetimibe (n = 6)	−26%
	Ezetimibe alone (n = 0)	–		Ezetimibe alone (n = 0)	–
	Statin alone (n = 1)	−9%		Statin alone (n = 0)	–

T12w Time 12 weeks; **T36w** Time 36 weeks; **He** heterozygous; **Ho** homozygous; **MLLT** maximal lipid lowering therapy; **LDL-C %** percent changes in low density lipoprotein cholesterol.

[a] One patient in this subgroup was excluded by the analysis because reporting total lipid lowering therapy withdrawal.

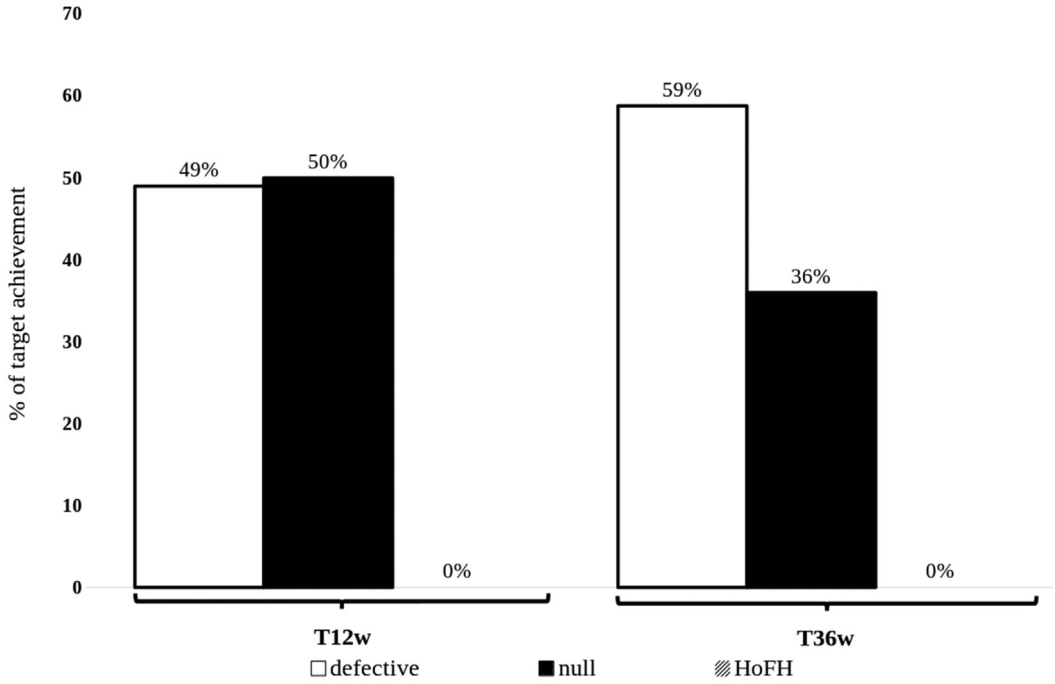

Figure 3 Percentage of low-density lipoprotein cholesterol (LDL-C) target achievement stratified according to genotype. Abbreviations:T12w Time 12 weeks; **T36w** Time 36 weeks; **HoFH** homozygous familial hypercholesterolemia.

was not influenced by background therapy but, more likely, by the dramatically impaired LDLR function.

On the other hand, concomitant statin + ezetimibe therapy was used by ≈ 75% of both He-defective and He-null FH subjects treated with PCSK9-I. Interestingly, He-null showed a similar LDL-C reduction than He-defective both at T12w and at T36w assessment. Although some evidence from previous studies suggested that He-null naïve subjects had higher LDL-C levels than He-defective naïve [33–35] in our analysis, we observed no difference in LDL-C baseline levels between He-null and He-defective subjects already receiving MLLT. Thus, the presence of a standard lipid lowering therapy seems to be able to reduce the difference in LDL-C between He-null and He-defective subjects observed in the naïve setting.

Remarkably, we found a reduction in LDL-C even in patient with statin or ezetimibe intolerance. However, it is noteworthy that subjects treated with single drug therapy (statin alone or ezetimibe alone), showed higher baseline LDL-C levels than patients treated with statin + ezetimibe. When adding a PCSK9-I treatment, subjects treated with single drug therapy reported a more marked reduction in LDL-C levels. This is likely due to the lack of a background treatment based on a synergistic interaction between statin and ezetimibe [36]. This makes PCSK9-I treatment proportionally more efficacious.

Among statin-treated subjects a further mechanism deserves to be discussed. A possible synergistic effect between statins and PCSK9-I has been described [37] and supported by previous studies showing that PCSK9-I reduced LDL-C levels of about 50% when used alone and about 70% when used together with statins [11,12]. In fact, patients chronically treated with statins showed increased PCSK9 plasma levels. This effect is secondary to the activation of sterol responsive element binding protein (SREBP) pathway because of the inhibition of cholesterol biosynthesis [12].

A further clinically relevant aspect is represented by LDL-C target achievement rate. In overall population, LDL-C target was achieved by 43% of subjects at T12w and by 44% at T36w. It is interesting to observe that, despite a significant LDL-C levels reduction, LDL-C target is achieved in <45% of cases. However, the influence of genotype should be considered. In fact, LDL-C target achievement was found in none of subjects with compound-He/Ho-FH, and in ≈50% of He-FH. This should be contextualized in the frame of the very ambitious LDL-C targets suggested by latest ESC/EAS guidelines [2]. Indeed, in our preliminary report, when considering targets suggested by 2016 ESC/EAS guidelines [38], LDL-C target was achieved by > 70% of He-FH [39].

In the present study we reported high adherence to therapy with PCSK9-I, thus suggesting a good tolerability profile of such a treatment. Adherence to MLLT represents a major clinical challenge in real world settings [40]. From this point of view, because of the proven efficacy, good safety profile and the high degree of compliance, PCSK9-I treatment could become a milestone for the therapeutic approach in FH patients.

Some potential limitations of our study should be mentioned. The relatively small sample size might limit reliability of our sub-group analyses. However, FH is a rare disease, especially compound-He/Ho form. In addition, guidelines for prescription of PCSK9-I therapy and

eligibility criteria in our Country are quite conservative. Thus, our results could be considered as an intriguing proof of concept for future ad hoc designed studies.

A further limitation is the lack of routine screening for mutation in *APOB and PCSK9* genes for all included subjects. On this hand, it is relevant to highlight that about 90% of FH cases are related to *LDLR gene* mutation [4]. In addition, the indication to proceed with *APOB and PCSK9* genes assessment is based on clinical suspicion. This is in line with the real-word approach of our study.

Further dedicated studies are necessary to evaluate impact of all FH causative mutations on therapeutic response to PCSK9-I.

In conclusion, PCSK9-I therapy showed a high efficacy profile both in He-null and in He-defective FH subjects, with a >50% LDL-C levels reduction. Response to therapy was significantly lower in compound-He/Ho-FH subjects, with a ≈20% LDL-C levels reduction being documented.

Overall, target achievement rate still represents a major issue in FH patients despite high efficacy profile of currently available lipid lowering strategies.

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Declaration of competing interest

All the authors have nothing to declare.

The protocol was approved by Federico II University local ethic Committee (approval code 2015/261).

The present study is an extension of the study with ClinicalTrials.gov identifier NCT04313270.

Acknowledgment

a preliminary report of the present study was presented as oral communication at 2020 ESC congress.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2021.10.025.

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