SciForschen
Open HUB for Scientific Research

ISSN 2379-769X

Journal of Heart Health

Review Article | Volume: 3.2 | Open Access

Statins: Their 3 Main Limitations The Whys of MAbs-PCSK9

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Received date: 06 Jan 2017; **Accepted date:** 08 Feb 2017; **Published date:** 14 Feb 2017.

Citation: Morales-Villegas EC (2017) Statins: Their 3 Main Limitations The Whys of MAbs-PCSK9. J Hear Health 3(2): doi http://dx.doi.org/10.16966/2379-769X.133

Abstract

This review analyses three of the most relevant statins therapeutic limitations, named familial hypercholesterolemia, high risk and statins therapeutic variability and statins muscular-intolerance. Familial hypercholesterolemia has been the engine for important discoveries such as LDLR and statins; the use of these has changed the natural history of ASCVD in these individuals. However, for subjects with the homozygous and to a lesser extent for individuals with the heterozygous forms, the therapeutic effect of statins is not sufficient to achieve optimal levels of LDL-cholesterol; in this paper, we will review the etiology, prevalence, diagnosis, evolution, treatment and new therapeutic options for this disease. Therapeutic variability is a very common clinical issue, in a given population, the administration of a statin of medium or high intensity reduces on average 30% or 50% the level of LDL-cholesterol. However, there is wide inter-individual and intra-individual variability in treatment with any HMGCoAR inhibitor. Both types of variability have prognostic implications and therefore their knowledge is important. The transcendence of the inter- and intra-individual therapeutic variability of statins supports the personalized approach in their use and justifies in a variable percentage the potential use of the MAbs-PCSK9, especially in high and very high risk individuals. Finally, since statin intolerance is a nonspecific concept wich may include muscle (myalgias and CPK increase) or non-muscle related (AST-ALT increase, neurocognitive abnormalities, gastrointestinal symptoms, etc.) adverse events associated with HMGCoAR inhibitors; in order to be more specific, the term Statin-Associated Muscle Symptoms or SAMS has been proposed. The reported prevalence of this problem varies widely from 30% in observational studies to <10% in "double-blind" studies. Statin muscle-intolerance is the most common cause for treatment discontinuation and is in turn an important risk factor for ASCVD, because that, it is essential to establish a correct diagnosis of SAMS and efficient alternative therapeutic strategies; thus, SAMS is another important and potential therapeutic "niche" for MAbs-PCSK9 commented in this review.

Keywords: Statins; MAbs-PCSK9; HMGCoAR

Abbreviations: FH: Familial Hypercholesterolaemia; LDLR: Low Density Lipoprotein Receptor; ASCVD: Atherosclerotic Cardiovascular Disease; HoFH: Homozygous Familial Hypercholesterolemia; HeFH: Heterozygous Familial Hypercholesterolemia; LDL: Low Density Lipoprotein; ER/GA: Endoplasmic reticulum /Golgi apparatus; apoB100: Apolipoprotein B100; PCSK9: Proprotein Convertase Subtilisin Kexin type 9; LDLRAP1: LDLR Adaptor Protein 1; Non-FH: Non-Familial Hypercholesterolemia; HMGCoAR: Hydroxy-methyl-glutaryl-coenzyme A reductase; VLDL: Very Low Density Lipoprotein; IDL: Intermediate density lipoprotein; ASO: Antisense Oligonucleotide; Lp (a): Lipoprotein little-a; REMS: Risk Evaluation and Mitigation Strategy; MTP: Microsomal Transfer Protein; CPK: Creatine Phosphokinase

Familial Hypercholesterolemia-An Undeniable Unmet Need

Etiology

FH determines a phenotype characterized by LDL cholesterol levels ≥ 200 mg/dL (≥ 5.2 mmol/L), cholesterol deposition in extravascular tissues, xanthomas, xanthelasmas, corneal arch and early ASCVD [1]. Goldstein and Brown documented for the first time that mutations in the LDLR gene -located on chromosome 19 - were the cause of the FH phenotype; these mutations can occur in both alleles of the LDLR gene encoding the receptor, giving rise to the homozygous genotype of FH or in a single allele, giving rise to the heterozygous genotype of FH [2].

More than one thousand mutations have been described in the LDLR gene [3]. From a functional point of view these mutations have been classified as type 1 with total failure in the synthesis of LDLR; type 2 with failure in the migration of LDLR from the ER/GA system to the cell membrane; Type 3 with failure in apoB100 recognition (LDLR ligand); Type 4 with failure in the internalization of the binomial LDLR/LDL and type 5 with failure in the dissociation of the binomial LDLR/LDL [3]. While approximately 90%-95% of the mutations causing the FH-phenotype are "classical" mutations of the LDLR gene, mutations have been documented in genes encoding other molecules involved in cellular cholesterol metabolism. In order of frequency: mutations in the APOB gene (~5%), located on chromosome 2 encoding apoB100 synthesis (LDLR ligand) [4]; mutations in the PCSK9 gene (~1%), located on chromosome 1 encoding PCSK9 synthesis with "gain of function" (protease facilitating intracellular proteolysis of LDLR) [5], and mutations in the LDLRAP1 gene (<1%), located on chromosome 1 encoding AP1 synthesis (LDLR adaptor protein 1 to cell membrane) [6]. The combination of these mutations may give rise to different FH genotypes, including: true HoFH by mutation of the same gene in both alleles (e.g., LDLR/LDLR), compound HoFH by mutation of a different gene in each allele (e.g., LDLR/PCSK9 "gain of function"), simple HeFH by mutation of a gene in one allele (e.g., APOB) and double HeFH by mutation of two genes in one allele (e.g., LDLR/APOB). The "malignancy" of the FH-phenotype is determined primarily by the affected number of alleles, the number and type of affected genes and the functional repercussion of the mutation as a whole [7]. Currently, these seemingly theoretical considerations are of great importance in the therapeutic efficacy and selection, especially in individual with HoFH [8-9].

Prevalence

Traditionally it has been established that the average prevalence of HoFH and HeFH is 1 case in 1 million and 1 case in 500 inhabitants, respectively [2]. These statistics have recently been "challenged" by the Dutch school of FH, who have reported that the prevalence of HoFH and HeFH can be up to 1 case in 160,000 and 1 case in 200 inhabitants, respectively [10-11]. Regardless of the actual prevalence of FH, as discussed below, the main problem in this pathology is the very low detection of cases [12].

Diagnosis

According to a recent FH registry, in countries like Holland or Norway, between 50% and 70% of individuals with FH are diagnosed, in contrast, in countries like Mexico or Brazil, this figure is less than 1% [12]. The diagnosis of HoFH is established by the genetic typing of two mutant alleles or the presence of severe hypercholesterolemia with LDL-cholesterol levels ≥ 500 mg/dL (≥ 13 mmol/L) in the absence of treatment or ≥ 300 mg/dL (≥ 7.2 mmol/L) on treatment plus xanthomas before age 10 and/or when both parents have HeFH. The diagnosis of HeFH is also established with the genetic typing of a mutant allele or with the sum of criteria of family history, personal history, exploratory signs, laboratory data and genetic typing (Dutch Lipid Clinic Network criteria or Simon Broome criteria) [10-12].

Evolution

The evolution of FH is determined by the level of hypercholesterolemia; in average terms, the "naïve" phenotypes of HoFH and HeFH are characterized respectively by LDL-cholesterol levels ≥ 500 mg/dL (≥ 13 mmol/L) and between 200-500 mg/dL (5.2-13 mmol/L), this determines that the burden of circulating LDL-cholesterol for the onset of an ASCVD (clinical threshold for ASCVD) is on average at 12.5 years and at 35 years of age, respectively; unlike FH, in Non-FH, even in the presence of other risk factors, the LDL-cholesterol level is <200 mg/dL (<5.2 mmol/L) and the occurrence of an ASCVD presents on average between 55-65 years of age [7,10-12].

Treatment

Although FH has a genetic etiology, to date its treatment is focused on the control of its biochemical subrogate, hypercholesterolemia. Without denying the contribution of indispensable hygienic-dietary measures, potent HMGCoR inhibitors or statins as atorvastatin and rosuvastatin have been the mainstay of treatment in FH. Vermissen reported in a cohort of more than two thousand individuals with FH followed for 10 years, a risk reduction for coronary heart disease of 76% (82-70% with P<0.001) in individuals treated with statins versus no-statins [13]. Even in individuals with HoFH, statins have been very important. Raal reported that statin therapy, since 1990, significantly increased the clinical threshold for cardiovascular death and for any type of ASCVD in individuals with HoFH, this apparently paradoxical event in HoFH is explained by the presence of residual LDLR (>2% to 25%) function in a significant percentage of these individuals, in addition to the statins inhibitory effect of VLDL synthesis and therefore the reduction effect of the IDL and LDL level, as well as by the potential pleiotropic actions of statins [14].

Pharmacological treatment for HoFH

As complementary therapies for statins, for non-statins lipid-lowering drugs (ezetimibe, resins, niacin) and even for apheresis, the following molecules have been investigated and approved in the HoFH for clinical use.

a) Mipomersen: It is an OAS silencing the messenger RNA encoding the synthesis of apoB100; this way by preferentially inhibiting hepatic synthesis of apoB100, inhibits the lipidation and synthesis of VLDL and in consequence reduces significantly the IDL and LDL circulatory level [15]. Mipomersen 200 mg S.C/week reduces on average 25% the level of LDL-cholesterol and other lipoproteins with apoB100, including Lp(a). The main adverse effects of mipomersen are, injection site skin reaction (76%), flu-like syndrome (29%) and elevated transaminases associated with fatty infiltration of the liver (12%); its prescription is approved under the REMS system [15-17].

b) Lomitapide: It is a small molecule inhibiting MTP, a lipid-transfer protein, especially triglycerides towards the apoprotein structure of chylomicrons (apoB48) and VLDL (apoB100); thus, by inhibiting its lipidation, it inhibits the synthesis of chylomicrons and VLDL, precursor lipoproteins of chylomicrons remmanents, IDL and LDL [18]. Under a strict diet with a very low fat content, oral lomitapide 5-60 mg/day reduces on average 40% the level of LDL-cholesterol and other lipoproteins with apoB100 without a significant reduction of Lp(a). The main adverse effects of lomitapide are gastrointestinal, associated with fatty gastrointestinal infiltration (>50%), flu-like syndrome (7%) and elevated transaminases associated with fatty infiltration of the liver (7%); like mipomersen, lomitapide prescription is approved under the REMS system [18].

c) Evolocumab: The MAb-PCSK9 evolocumab at 420 mg S.C/4 weeks is approved in the United States, the European Union and Mexico for clinical use in individuals ≥ 12 years of age with HoFH [19-20]. In this population, evolocumab reduces LDL-cholesterol and other lipoproteins with apoB100 significantly, especially in individuals with HoFH with residual LDLR function (>2% to 25%); the safety and tolerability profile of evolocumab is similar to placebo [8-9].

In the TESLA-B trial [9], individuals with HoFH receiving lipid-lowering treatment and not on apheresis, evolocumab compared to placebo reduced ultracentrifugation LDL-cholesterol by 30.9% (95% CI 43.9% to 18.0%: P<0.0001) and apolipoprotein-B100 by 23.1% (95% CI 34.8 to 11.5%: P 0.002). It is relevant to note that LDL-cholesterol responses were according to LDLR residual function; patients with LDLR negative mutations in both alleles and one patient with autosomal recessive HoFH showed no response to evolocumab, whereas in patients with LDLR mutations in both alleles of which at least one was defective the LDL-cholesterol reduction was 40.8%. In this cohort of patients with very high levels of Lp(a), the overall reduction in this lipoprotein did not reach statistical significance (11.8% with 95% CI -25.5% to 1.8: P 0.09). The safety and tolerability profile of evolocumab was similar to placebo.

Pharmacological treatment for HeFH

As complementary therapies for statins, for non-statins lipid-lowering drugs (ezetimibe, resins and niacin), the following molecules have been investigated and approved in the HeFH for clinical use.

a) Evolocumab: It is approved in the United States, the European Union and Mexico [19-20] for therapeutic use in HeFH at doses of 140 mg S.C/2 weeks or 420 mg S.C/4 weeks as an adjuvant therapy to statins and/or other non-statins lipid-lowering drugs when LDL-cholesterol is not in the therapeutic target [19]. Currently, a level of LDL- cholesterol <100 mg/dL (<2.6 mmol/L) in primary prevention and <70 mg/dL (<1.8 mmol/L) in secondary prevention is accepted as a therapeutic target in HeFH [21,22]. Based on the positive results from evolocumab phase I and II studies, study RUTHERFORD-2 [23], included 331 individuals with HeFH on steady-dose statin therapy with or without other non-statins lipid-lowering drugs with LDL-cholesterol ≥ 100 mg/dl (≥ 2.6 mmol/L). The authors reported that evolocumab 140 mg S.C/2 weeks and 420 mg S.C/4 weeks versus placebo determined a reduction of LDL-cholesterol of 59.2% and 61.3% respectively, both with a P value of <0.0001. Compared with 2% in the placebo group, in the evolocumab 140 mg S.C/2 weeks and 420 mg S.C/4 weeks groups, 68.0% and 63% of the individuals achieved LDL-cholesterol levels <70 mg/dL (<1.8 mmol/L). Adverse events of treatment with evolocumab, including injection site reaction as a reason for discontinuation, did not differ significantly from those reported with

placebo. The response to evolocumab was not influenced by the type of mutation associated with HeFH [23].

b) Alirocumab: It is approved in the United States, the European Union and Mexico [20,24] for therapeutic use in HeFH at doses of 75 or 150 mg S.C/2 weeks as an adjuvant therapy to statins and/or other non-statins lipid-lowering drugs when LDL-cholesterol is not in the therapeutic target. Based on the positive results of Phase I and II studies with alirocumab, study ODYSSEY FH I and study ODYSSEY FH II [25], included 486 and 246 individuals with HeFH on high-intensity statins at a high-dose or a maximum tolerated dose with LDL-cholesterol levels ≥ 70 mg/dl (≥ 1.8 mmol/L) (secondary prevention) or ≥ 100 mg dL (≥ 2.6 mmol/L) (primary prevention). The authors of ODYSSEY FH I and II respectively reported that alirocumab 75-150 mg S.C/2 weeks versus placebo determined a reduction of LDL-cholesterol from 144.7 mg/dL to 71.3 mg/dL, equivalent to a reduction of 57.9% and 134.6 mg/dL to 67.7 mg/dL, equivalent to a reduction of 51.4%, both with a P value of <0.0001. This therapeutic effect was sustained during the 78 weeks of follow-up; 72.2% versus 2.4% and 81.4% versus 11.3% of individuals reached an LDL-cholesterol level <100 or <70 mg/dL (<2.8 or <1.8 mmol/L) (primary or secondary prevention) and 59.8% versus 0.8% and 68.2% versus 1.2% reached an LDL-cholesterol level of <70 mg/dL (<1.8 mmol/L). Adverse events of treatment with alirocumab, including injection site reaction as a reason for discontinuation, did not differ significantly from those reported with placebo. This court of individuals is being followed for 3 years in a voluntary and open design [25].

An "*in vitro*" study with alirocumab in lymphocytes of individuals with autosomal recessive familial hypercholesterolemia (ARH) was recently published; the results of this study demonstrated a favorable potential effect on LDLR expression in this population [26].

As can be derived from the RUTHERFORD-2 and ODYSSEY FH-I-II studies in HeFH, a condition in which only 25% of individuals achieve the therapeutic targets with statin-based therapy and/or other non-statins lipid-lowering drugs, the addition of a MAb-PCSK9 such as evolocumab or alirocumab allows those numbers to be reversed. On average 75% and 60% of HeFH individuals reach LDL-cholesterol levels <100 mg/dL (<2.6 mmol/L) and <70 mg/dL (<1.8 mmol/L) respectively when a MAb-PCSK9 is added to the treatment; this response is not influenced by the type of mutation associated, so in HeFH, genotyping has no therapeutic relevance [23,25].

c) Other molecules in clinical research: Inclisiran, a lipid nano-particle (ALN-PCS) conjugated with N-acetyl-galactosamine is a small molecule avidly captured by hepatic asialo-glycoprotein receptors [27]. This molecule currently in phase III, inhibits by interference the mRNA dictating the translation for the PCSK9 synthesis and thus reducing its circulating levels significantly, until now with a significant efficacy (LDL-cholesterol reduction 35% to 50%) and very favorable safety and tolerability profile [28-29]. Bempedoic acid (ETC-1002), an inhibitor of sterol and fatty-acid synthesis and enhancer of fatty-acid oxidation by inhibition of adenosine-triphosphate citrate lyase and activation of adenosine monophosphate-activated protein kinase [30], is a molecule currently in phase III. ETC-1002 reduces efficiently the LDL-cholesterol level (25-30%) with a favorable safety and tolerability profile [31-33].

High Risk and Therapeutic Variability-Another Risk Factor

Although the CTT meta-analyzes 2005 [34] and 2010 [35] established that a medium- or high- intensity statin determines an average LDL-cholesterol reduction of 30% and 50% respectively, the individual response has wide inter- and intra-individual variability [36,37]. The first implies that between individuals the therapeutic response to the same statin and dose is different and the second implies that in the same individual the therapeutic response to the same statin and dose may vary throughout the treatment.

Inter-individual variability

In 2014, Boekholdt, Kastelein et al. [36]. published an "individual-by-individual" meta-analysis of eight RCTs with statins. This meta-analysis included 38,153 individuals treated with statins, 155,573 person-years of follow-up, and 5,387 major incident cardiovascular events -14.1%-. The meta-analysis objectives were, to determine the inter-individual variability in the treatment with statins, to determine the percentage of individuals achieving the target for LDL-cholesterol, non-HDL-cholesterol and apolipoprotein-B100 during high intensity-statin therapy and to determine the therapeutic benefit of different LDL-cholesterol levels during treatment with statins.

The inter-individual variability analysis with the statin therapy showed a "waterfall" distribution. Regardless of the statin and/or its intensity, the therapeutic response to a same statin and dose was characterized by a continuum, from minimal to maximum individual response, for both LDL-cholesterol and non-HDL-cholesterol and for apolipoprotein-B100. In the analysis of the percentage of individuals achieving the target for LDL-cholesterol during treatment with high-intensity statins, 12, 40 and 78% of individuals did not achieve values of <100, <70 and <50 mg/dL; these figures were similar and proportional when the non-HDL-cholesterol and apolipoprotein-B100 were analyzed. Finally, in the analysis of the therapeutic benefit of different levels of LDL-cholesterol, the maximum therapeutic benefit was observed for the level of <50 mg/dL with 0.44 and 0.81 HR for any major cardiovascular event, compared to levels of 175 and 75-100 mg/dL respectively; in the same line, these figures were similar when the non-HDL-cholesterol and apolipoprotein-B100 were analyzed.

In their discussion, the authors review the potential causes for the large interindividual variability in the response to statin therapy, among others sex, age, smoking status, body weight, diet, physical activity, genetic variants and the multifactorial and very prevalent non-adherence. Finally, they conclude that their results support the guidelines recommendation to monitor the response of each individual throughout the treatment with a given statin [37-39], and justify the research of adjuvant therapies to statins facilitating the achievement and maintenance of stable and appropriate LDL-cholesterol levels for each individual, currently in development [40].

Intra-individual variability

With the aim of knowing if visit-to-visit variability in LDL-cholesterol affects future cardiovascular outcomes, in 2015, Bangalore and colleagues published their "post-hoc" analysis of the TNT study cohort on intra-individual variability during treatment with atorvastatin in individuals with ASCVD [41]. In this analysis of 9,572 individuals with ASCVD treated with atorvastatin 10 or 80 mg/day, the authors reported that variation greater than one standard deviation in LDL-cholesterol during treatment with atorvastatin determines a significant increase in the risk of any major cardiovascular event: 23% death, 17% stroke, 16% any coronary event, 11% any cardiovascular event, and 10% myocardial infarction. Intra-individual variability quantified by different methods and after multivariate adjustment proved to be an independent variable with an inversely proportional relation to treatment intensity -atorvastatin 80 mg has lower intra-individual variability than atorvastatin 10 mg- and is probably related to the pleiotropism of HMGCoAR inhibitors [41].

Based on this analysis and beyond the reported intra-individual variability variability explained by statin treatment non-adherence [42], the authors argue that regardless of LDL-cholesterol lowering efficacy, consistency in LDL-cholesterol reduction should be a parallel goal. As for inter-individual variability, these observations justify the need to monitor the response of each individual throughout the treatment with

a given statin [37-39], justify the research of adjuvant therapies to statins facilitating the achievement and maintenance of stable and appropriate LDL-cholesterol levels for each individual [40], and also support the re-analysis of some recommended strategies for intermittent statin therapy, especially for suspected statin intolerance [43].

Muscle Statin Intolerance or SAMS-Frequent Cause for Discontinuation

Statin intolerance is a nonspecific concept since it may include muscle (myalgias and CPK increase) or non-muscle related (AST-ALT increase, neurocognitive abnormalities, gastrointestinal symptoms, etc.) adverse events associated with HMGCoAR inhibitors; therefore, in order to be more specific, the term Statin-Associated Muscle Symptoms or SAMS has been proposed [44]. The prevalence of SAMS is variable; in observational studies, the prevalence ranges from 15 to 30% [45,46]; however, in the only "double-blind" study designed to assess the impact of statins on muscle function -STOMP-, the prevalence is <10%, with a marginally significant difference compared to placebo, similar to that reported in statin clinical studies [47].

Even in populations such as the European or American, non-adherence to treatment with statins is a frequent situation -46%- and SAMS are the most common cause -60%- [48]. In developing countries, non-adherence to statins is greater than 90% [49]. This situation is of great clinical importance since the non-adherence to the treatment with statins is associated to a significant increase of cardiovascular morbidity and mortality -HR up to 1.45- [48]. Therefore, avoiding treatment interruption of statins for "pseudo-intolerance" is a task to be fulfilled by all prescribing physicians and for this purpose in Lat-Am we have updated the most important clinical concepts of this construct called SAMS [50].

Diagnosis

For the diagnosis of SAMS, three criteria are fundamental. The criterion defining construct, muscular symptoms, which are generally symmetrical, proximal and large muscle group myalgias; the one defining severity, CPK elevation, for which there are different cut points: <3x uln or mild, 3-7x uln or moderate and >7x uln or severe; the one defining causality, chronology, which is generally a criterion not considered, but it is of great relevance; SAMS usually occur 4-12 weeks after initiation of statin therapy, they are associated or increased with intense muscle activity and have a positive pattern to challenge - initiated administration -, to challenge suspension - interruption - and to counterchallenge - resumed administration – [50]. There are multiple risk factors or conditions favoring SAMS, among them the most frequent are, pharmacological interaction, fragility syndrome, low body mass index, female sex, smoking, alcoholism, cocaine use, thyroid, renal, hepatic and/or muscular diseases (myopathy). Together with the clinical history of basal musculoskeletal and articular conditions, the documentation of such predisposing factors of SAMS is fundamental in every individual candidate for treatment with statins [43,44,50].

Classification

Based on the clinical presentation and CPK level, the following SAMS classification has been proposed. Grade 0: asymptomatic and CPK <3x uln; Grade I: tolerable myalgia and CPK <3x uln; Grade 2: intolerable myalgia and CPK <3x uln; Grade 4: myalgia and CPK between 3-7x uln; Grade 5: rhabdomyolysis and Grade 6: necrotizing autoimmune myositis. This classification is useful for homogenizing criteria and regulating therapeutic strategies. Accepted criteria for the diagnosis of rhabdomyolysis are: asymptomatic increase of CPK >50x uln or symptomatic increase of CPK >10x uln, both with increased creatinine >0.5 mg/dL and myoglobinuria; necrotizing autoimmune myositis is a very rare pathology associated with antibodies against HMGCoAR [43,44,50]. The term statin intolerance secondary to SAMS should include the following characteristics: a) SAMS with at least two statins at any dose or at doses lower than 5, 10, 20, 20, 20 or 40 mg/day of rosuvastatin, atorvastatin, simvastatin, pravastatin, lovastatin or fluvastatin, respectively; b) intolerable myalgia even with mild elevated CPK or tolerable myalgia with CPK elevation >7x uln, and c) a positive pattern to challenge, challenge suspension and counterchallenge [43,44,50].

Treatment

Once the actual intolerance to statins by SAMS has been confirmed, its treatment is the interruption of HMGCoAR inhibitors or the use of the minimum tolerated dose; the treatment of rhabdomyolysis and necrotizing autoimmune myositis is out of the focus of this review. On the other hand, hypercholesterolemia treatment and control of atherosclerotic cardiovascular risk leading to the use of statins, will be in function of the magnitude of the SAMS and the atherosclerotic cardiovascular risk; for a 0-1 degree SAMS with a high cardiovascular risk, the use of the statin at the maximum tolerated dose and, where appropriate, an adjuvant non-statin drug, would be an appropriate approach; for a grade 2 or higher SAMS, statin discontinuation is required and the alternative use of non-statin drugs will be based on the availability and level of atherosclerotic cardiovascular risk -ezetimibe, fibrates, exchange resins, etc. [43,44,50].

MAbs-PCSK9 in SAMS

In individuals with actual statin intolerance by SAMS and high atherosclerotic cardiovascular risk, MAbs-PCSK9 have one of their most important therapeutic "niches". In individuals with statin intolerance by SAMS under the criterion of intolerance to any dose of two statins or the inability to tolerate increases at the minimal therapeutic doses of two statins, the ODYSSEY Alternative studies with alirocumab 150 mg S.C/2 weeks [51] and GAUSS-2 and GAUSS-3 [52-53], with evolocumab 140 mg S.C/2 weeks or 420 mg S.C/4 weeks, showed a high efficacy in this population - >50% - and superior to ezetimibe for LDL-cholesterol reduction with an excellent safety and tolerability profile. Thus, MAbs-PCSK9 are outlined as one of the most important options to meet this therapeutic need, especially in individuals with a high and very high atherosclerotic cardiovascular risk [37,38].

References

1. Khachadurian AK (1964) The inheritance of essential familial hypercholesterolemia. Am J Med 37: 402-407.
2. Brown MS, Goldstein JL (1985) A receptor-mediated pathway for cholesterol homeostasis. Science 232: 34-47.
3. Aguilar-Salinas C, Gómez-Diaz RA, Gómez-Pérez FJ (2008) Diagnostic Approach to Dyslipidemias in Clinical to Molecular Dyslipidemias. Capítulo 3: 102-114.
4. Soria LF, Ludwing EH, Clarke HR, Vega GL, Grundy SM, et al. (1989) Association between a specific apoprotein B mutation and familial defective apo B100. Proc Natl Acad Sci U S A 86: 587-591.
5. Abifadel M, Varret M, Rabes JP, Boileau C, Benjannet S, et al. (2003) Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nature Genetics 34: 154-156.
6. Garcia CK, Wilund K, Arca M, Zuliani G, Fellin R, et al. (2001) Autosommal recessive hypercholesterolemia caused by mutations in a putative LDL receptor adaptor protein. Science 292: 1394-1398.
7. Raal FJ, Santos RD (2012) Homozygous familial hypercholesterolemia: Current perspectives on diagnosis and treatment. Atherosclerosis 223: 262- 268.

8. Stein EA, Honarpour N, Wasserman SM, Xu F, Scott R, et al. (2013) Effect of the proprotein convertase subtilisin/kexin 9 monoclonal antibody, AMG 145, in homozygous familial hypercholesterolemia. Circulation 128: 2113-2120.

9. Raal FJ, Honarpour N, Blom DJ, Hovingh GK, Xu F, et al. (2015) Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolemia (TESLA part B): a randomized, double-blind, placebo-controlled trial. Lancet 385: 341-350.

10. Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, et al. (2014) Homocygous familial hypercholesterolemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolemia of the European Atherosclerosis Society. Eur Heart J 35: 2146-2157.

11. Sjouke B, Kusters DM, Kindt I, Besseling J, Defesche JC, et al. (2015) Homocygous autosomal dominant hypercholesterolemia in Netherlands: Prevalence, genotype-phenotype relationship and clinical outcome. Eur Heart J 36: 560-565.

12. Nordestgaard BG, Chapman MJ, Humphries ST, Ginsberg HN, Masana L, et al. (2013) Familial hypercholesterolemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. Eur Heart J 34: 3478-3490.

13. Versmissen J, Ooterveer DM, Yazdanpanah M, Defesche JC, Basart DC, et al. (2008) Efficacy of statins in familial hypercholesterolemia: a long term cohort study. BMJ 337: a2423.

14. Raal FJ, Pilcher GJ, Panz VR, Van Deventer HE, Brice BC, et al. (2011) Reduction in mortality in subjects with homocygous familial hypercholesterolemia associated with advances in lipid lowering therapy. Circulation 124: 2202-2207.

15. Raal FJ, Santos RD, Blom DJ, Marais AD, Charng MJ, et al. (2010) Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL colesterol concentrations in patients with homocygous familial hypercholesterolemia: a randomized, double-blind, placebo-controlled trial. Lancet 375: 998-1006.

16. Akdim F, Tribble DL, Flaim JD, Yu R, Su J, et al. (2011) Efficacy of apolipoprotein B synthesis inhibition in subjects with mild-to-moderate hyperlipidemia. Eur Heart J 32: 2650-2659.

17. Stein EA, Dufour R, Gagne C, Gaudet D, East C, et al. (2012) Apolipoprotein B synthesis inhibition with Mipomersen in Heterocygous familial hypercholesterolemia: Results of a randomized, double-blind, placebo controlled trial to assess efficacy and safety as add-on therapy in patients with coronary artery disease. Circulation 126: 2283-2292.

18. Cuchel M, Meagher EA, Theron HT, Blom DJ, Marais AD, et al. (2013) Efficacy and safety of a microsomal trygliceride transfer protein inhibitor in patients with homocygous familial hypercholesterolemia: a single-arm, open-label, phase 3 study. Lancet 381: 40-46.

19. Markham A (2015) Evolocumab: First Global Approval. Drugs 75: 1567-1573.

20. COFEPRIS. Napoles, Mexico City, Mexico.

21. Landmesser U, Chapman MJ, Farnier M, Gencer B, Gielen S, et al. (2016) European Society of Cardiology/European Atherosclerosis Society Task Force consensus statement on proprotein convertase subtilisin/kexin type 9 inhibitors: practical guidance for use in patients at very high cardiovascular risk. Eur Heart J.

22. Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly DD Jr, et al. (2016) 2016 ACC Expert Consensus Decision Pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular risk. J Am Coll Cardiol 68: 92-113.

23. Raal FJ, Stein E, Dufour R, Turner T, Civeira F, et al. (2015) PCSK9 inhibition with evolocumab (AMG 145) in heterocygous familial hypercholesterolemia (RUTHERFORD-2): a randomized, double-blind, placebo-controlled trial. Lancet 385: 331-340.

24. Markham A (2015) Alirocumab: First Global Approval. Drugs 75: 1699-1705.

25. Kastelein JJP, Ginsberg HN, Langslet G, Hovingh GK, Ceska R, et al. (2015) ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterocygous familial hypercholesterolemia. Eur Heart J 36: 2996-3003.

26. Thedres A, Sjouke B, Passard M, Prampart-Fauvet S, Guédon A, et al. (2016) Proprotein Convertase Subtilisin Kexin Type 9 Inhibition for Autosomal Recessive Hypercholesterolemia-Brief Report. Atheroscler Thromb Vasc Biol 36: 1647-1650.

27. Nair JK, Willoughby JL, Chan A, Charisse K, Alam MR, et al. (2014) Multivalent N-acetylgalactosamine-conjugated siRNA localizes in hepatocytes and elicits robust RNAi-mediated gene silencing. J Am Chem Soc 136: 16958-16961.

28. Fitzgerald K, White S, Borodovsky A, Bettencourt BR, Strahs A, et al. (2017) A highly durable RNAi therapeutic inhibitor of PCSK9. New Engl J Med 376: 41-51.

29. Ray KK, Landmesser U, Leiter LA, Kallend D, Wijngaard P, et al. (2016) ORION-1. Inclisiran inhibits PCSK9 synthesis by RNA interference. Planned interim analysis of a multi-center randomized, controlled dose-finding trial. AHA Scientific Sessions, Late breaking presentation. The Medicines Company, New Jersey, USA.

30. Pinkosky SL, Filippov S, Srivastava RA, Hanselman JC, Bradshaw CD, et al. (2013) AMP-activated protein kinase and ATP-citrate lyase are two distinct molecular targets for ETC-1002, a novel small molecule regulator of lipid and carbohydrate metabolism. J Lipid Res 54: 134-135.

31. Ballantyne CM, Davidson MH, Macdougall DE, Bays HE, Dicarlo LA, et al. (2013) Efficacy and safety of a novel dual modulator of adenosine triphosphate-citrate lyase and adenosine monophosphate-activated protein kinase in patients with hypercholesterolemia: results of a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. J Am Coll Cardiol 62: 1154-1162.

32. Gutierrez MJ, Rosenberg NL, Macdougall DE, Hanselman JC, Margulies JR, et al. (2014) Efficacy and safety of ETC-1002, a novel investigational low-density lipoprotein-cholesterol-lowering therapy for the treatment of patients with hypercholesterolemia and type 2 diabetes mellitus. Arterioscler Thromb Vasc Biol 34: 676-683.

33. Thompson PD, Rubino J, Janik MJ, MacDougall DE, McBride SJ, et al. (2015) Use of ETC-1002 to treat hypercholesterolemia in patients with statin intolerance. J Clin Lipidol 9: 295-304.

34. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, et al. (2005) Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 366: 1267-1278.

35. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, et al. (2010) Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 376: 1670-1681.

36. Boekholdt SM, Hovingh GK, Mora S, Arsenault BJ, Amarenco P, et al. (2014) Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. J Am Coll Cardiol 64: 485-494.

37. Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly DD, et al. (2016) 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 68: 92-125.

38. Reiner Z, Catapano AL, Backer GD, Graham I, Taskinen MR, et al. (2016) ESC/EAS Guidelines for the management of dyslipidemias. The Task Force for the Management of Dyslipidemias of the ESC-EAS. Eur Heart J 32: 1769-1818.

39. Norma Oficial Mexicana (2012) NOM037-SSA2-2012. For the Prevention, Treatment and Control of Dyslipidemias. Rev Mex Cardiol 23: 91-124.

40. Morales-Villegas E (2017) PCSK9 Inhibition-Reaching Physiologic LDL-C levels "Endo, Goldstein and Brown´s Dream is Coming True. J Hear Health 3: 132.

41. Bangalore S, Breazna A, DeMicco DA, Wun CC, Messerli FH, et al. (2015) Visit-to-visit low-density lipoprotein cholesterol variability and risk of cardiovascular outcomes: insights from the TNT trial. J Am Coll Cardiol 65: 1539-1548.

42. Mann DM, Glazer NL, Winter M, Paasche-Orlow MK, Muntner P, et al. (2013) A pilot study identifying statin nonadherence with visit-to-visit variability of low-density lipoprotein cholesterol. Am J Cardiol 111: 1437-1442.

43. Mancini GB, Tashakkor AY, Baker S, Bergeron J, Fitchett D, et al. (2013) Diagnosis, prevention, and management of statin adverse effects and intolerance: Canadian Working Group Consensus update. Can J Cardiol 29: 1553-1568.

44. Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, et al. (2015) Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. Eur Heart J 36: 1012-1022.

45. El-Salem K, Ababneh B, Rudnicki S, Malkawi A, Alrefai A, et al. (2011) Prevalence and risk factors of muscle complications secondary to statins. Muscle Nerve 44: 877-881.

46. Hansen KE, Hildebrand JP, Ferguson EE, Stein JH (2005) Outcomes in 45 patients with statin-associated myopathy. Arch Intern Med 165: 2671-2676.

47. Parker BA, Capizzi JA, Grimaldi AS, Clarkson PM, Cole SM, et al. (2013) Effect of statins on skeletal muscle function. Circulation 127: 96-103.

48. Chowdhury R, Khan H, Heydon E, Shroufi A, Fahimi S, et al. (2013) Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J 34: 2940-2948.

49. Teo K, Chow CK, Vaz M, Rangarajan S, Yusuf S, et al. (2014) Prospective Urban Rural Epidemiologic (PURE) cohort study. N Engl J Med 371: 818-826.

50. Sposito AC, Rocha J, de Carvalho LS, Lorenzatti A, Cafferata A, et al. (2017) Statin-Associated Muscle Symptoms. Position paper from the Luso-Latin American Consortium. Curr Med Res and Opin 33: 239-251.

51. Moriarty PM, Thompson PD, Cannon CP, Guytonet JR Bergeronet J, et al. (2014) Efficacy and Safety of the Proprotein Convertase Subtilisin/kexin Type 9 Monoclonal Antibody, Alirocumab, versus Ezetimibe, in patients with Statin Intolerance as defined by a placebo run-in and statin rechallenge Arm -ODYSSEY ALTERNATIVE-. Circulation 130**:** 2105-2126.

52. Stroes E, Colquhoun D, Sullivan D, Civeira F, Rosenson RS, et al. (2014) Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance. The GAUSS-2 randomized, placebo-controlled, phase 3 clinical trial of evolocumab. J Am Coll Cardiol 63: 2541-2548.

53. Nissen SE, Stroes E, Dent-Acosta RE, Rosenson RS, Lehman SJ, et al. (2016) Efficacy and tolerability of Evolocumab vs Ezetimibe in patients with Muscle-Related Statin Intolerance. The GAUSS-3 randomized clinical trial. JAMA 315: 1580-1590.