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Inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9)
A new approach to lipid lowering treatment

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Αναστολή της PCSK9
Μια νέα προσέγγιση στην υπολιπιδαιμική αγωγή

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ABSTRACT: Cardiovascular disease is the single most common cause of death worldwide; hence its prevention constitutes a strategic target for the improvement of life expectancy and quality of life. Statins are an essential element of lipid lowering treatment for decades with undisputable benefits. However, there are patients who cannot tolerate statins or cannot achieve the goal of lipid lowering treatment only by statins. Studying people with genetically high or low cholesterol levels and the analysis of their genome has led to the discovery of the proprotein convertase subtilisin/kexin type 9 (PCSK9) protein. The important contribution of the PCSK9 to the catabolism of the low density lipoprotein (LDL) receptor renders it as the main regulator in cholesterol metabolism, thus making it an attractive target for the development of new drugs. Inhibiting the PCSK9 protein by using monoclonal antibodies is the most advanced approach, given that it achieves an additional reduction of LDL cholesterol by 50–60%, while having an excellent safety

ΠΕΡΙΛΗΨΗ: Τα καρδιαγγειακά νοσήματα αποτελούν την πρώτη αιτία θανάτου παγκοσμίως και η πρόληψή τους αποτελεί στρατηγικό στόχο για τη βελτίωση του προσδόκιμου επιβίωσης και της ποιότητας ζωής. Οι στατίνες αποτελούν τον θεμέλιο λίθο της υπολιπιδαιμικής αγωγής για δεκαετίες, με εντυπωσιακά αποτελέσματα στη μείωση της καρδιαγγειακής νοσηρότητας και θνητότητας. Ωστόσο υπάρχουν ασθενείς που δεν μπορούν να ανεχθούν τις στατίνες ή δεν μπορούν να επιτύχουν τον στόχο της υπολιπιδαιμικής αγωγής μόνο με στατίνες. Η μελέτη ατόμων με γενετικά αυξημένη ή μειωμένη χοληστερόλη και η ανάλυση του γονοτύπου τους οδήγησε στην ανακάλυψη της πρωτεΐνης proprotein convertase subtilisin/kexin type 9 (PCSK9). Η σημαντική συμμετοχή της πρωτεΐνης PCSK9 στον καταβολισμό του υποδοχέα των χαμηλής πυκνότητας λιποπρωτεϊνών (LDL υποδοχέα) την καθιστά κύριο ρυθμιστή του μεταβολισμού της χοληστερόλης και ως εκ τούτου ελκυστικό στόχο για την ανάπτυξη νέων φαρμάκων. Η αναστολή της PCSK9 με τη χρήση μονοκλωνικών αντισωμάτων αποτελεί

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profile. While waiting for more studies to be completed, it seems that we are witnessing a revolution in the fields of lipid lowering treatment and prevention of cardiovascular disease.

την προκρινόμενη προσέγγιση, δεδομένου ότι επιτυγχάνει επιπρόσθετες μειώσεις της χοληστερόλης των χαμηλής πυκνότητας λιποπρωτεϊνών (LDL χοληστερόλη) της τάξης του 50–60% με πολύ καλό προφίλ ασφάλειας. Εν αναμονή της ολοκλήρωσης μεγάλων μελετών, όλα δείχνουν ότι βρισκόμαστε ενώπιον μιας επανάστασης στον τομέα της υπολιπιδαιμικής αγωγής και της πρόληψης των καρδιαγγειακών νοσημάτων.

Key words: Protein PCSK9, LDL cholesterol, dyslipidemia, monoclonal antibody.

Λέξεις ευρετηρίου: Πρωτεΐνη PCSK9, LDL χοληστερόλη, δυσλιπιδαιμία, μονοκλωνικό αντίσωμα.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide and its incidence is expected to rise in the years to come.[1] Thus, both the scientific community and the national health systems have focused their interest on CVD prevention. Increased concentration of low density lipoprotein (LDL) cholesterol is a major risk factor for CVD incidents, while decreasing LDL cholesterol is a primary target of treatment. Statins are the basis of the hypolipidemic treatment by inhibiting 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, an essential enzyme in cholesterol's hepatic production. Statins are associated with impressive benefits in cardiovascular prevention. European Society of Cardiology/ European Atherosclerosis Society (ESC/EAS) guidelines suggest reducing LDL cholesterol levels to lower than 70 mg/dL for very high risk patients.[2] However, up to 80% of these patients fail to reach this target.[3,4] Many patients have familial hypercholesterolemia (FH) and therefore very high baseline LDL cholesterol levels and inability to achieve lipid targets with statin alone or even in combination with ezetimibe. Of note, patients receiving statins have a significant residual cardiovascular risk that underlines the need for more effective decrease of LDL cholesterol.[5,6] Moreover, 5–10% of patients cannot tolerate an effective or any dose of statins because of myopathy.[7,8] It is obvious that new, safe and effective drugs are needed.

2. LDL metabolism and the discovery of PCSK9

Our knowledge of LDL regulation was limited to the interaction between LDL particles and LDL receptors on the hepatic cells. Genetic mutations lowering LDL receptor activity are known to be responsible for a FH phenotype. Similarly, mutations in apolipoprotein B (ApoB) lead to FH. In 1999, Varret et al. reported for the first time a 3rd genetic locus, mutations of which result in FH.[9] This was concluded after studying a family in France who presented with autosomal dominant FH phenotype but had no mutations in LDL receptor and ApoB genes.[9] Further study showed in 2003 an association of a protein with the LDL receptor and LDL cholesterol levels.[10] This protein was named proprotein convertase subtilisin/kexin type 9 (PCSK9) and is the product of PCSK9 gene in chromosome 1p32.3. Two mutations of that gene were described, both resulting in autosomal dominant FH. In particular, 2 families with heterozygous FH (HeFH) and history of early CVD were studied and no genetic relation with the LDL receptor or ApoB was found. The genetic sequence analysis though, revealed mutations in PCSK9 gene that enhanced the protein's activity (gain-of-function mutations) and decreased LDL receptor function.[10]

Studies in mice followed, revealing that overexpression of PCSK9 protein (via a genetically modified adenovirus expressing the PCSK9 gene) leads to increased LDL cholesterol and a phenotype similar to that of mice with complete LDL receptor absence.[11] In addition, administering the PCSK9 protein to mice decreased LDL receptors on hepatic cell surface, without decreasing their mRNA.[11] In contrast, deleting the PCSK9 gene from mice genome increased LDL receptors and reduced LDL cholesterol by increasing its hepatic clearance.[12]

In humans, it was found that PCSK9 mutations resulting in decreased activity of PCSK9 (loss-of-function mutations) are associated with decreased LDL cholesterol levels. Two mutations of the PCSK9 gene, present in 2% of the blacks, decrease LDL cholesterol up to 40%,

while another mutation, present in 3.2% of the whites, decreases LDL cholesterol up to 21%.

Studying the carriers of these mutations, it was found that a decrease of LDL cholesterol by 40 mg/dL, attributed to PCSK9 mutations, is related with an 88% reduction of coronary artery disease.[13] This benefit is much greater in comparison to the benefit seen in statin trials for similar LDL cholesterol reductions, likely because the low LDL cholesterol levels exist for a lifetime.[13] A meta-analysis of 312,312 people studied 9 genetic polymorphisms (SNPs) responsible for a long standing reduction of LDL cholesterol. It was found that for every 38.7 mg/dL of long standing LDL cholesterol reduction, CVD risk decreases by 54.5%. The same decrease of LDL cholesterol with statins is associated with a CVD risk reduction of 24%.[14] Thus, when LDL cholesterol is low since very early in life, CVD risk is 3 times lower compared with the statin-induced risk reduction later in life.

3. The role of PCSK9 in LDL receptor metabolism

In what way does PCSK9 affect serum LDL cholesterol levels? PSCK9 protein, consisted by 692 amino-acids, interacts directly with the extracellular section of LDL receptor (EGF-A sector) and forms a complex which is then internalized via clathrin-coated pits. In the acidic environment of the endosome, the interaction between PCSK9 and LDL receptor increases, as their bond becomes stronger (by 150–170 times). Thus, PCSK9 inhibits the recycle of LDL receptor to the cellular surface, promoting its degradation by lysosomal hydrolases.[15] Consequently, in the presence of PCSK9 LDL receptor degradation is augmented, decreasing their density on the cellular surface and resulting in decreased hepatic LDL uptake and increased serum LDL cholesterol levels.

In the general population, PCSK9 protein shows a large range of serum concentrations (33–2988 ng/mL).[16] Trying to discover the determinants of PCSK9 levels, it was found that women have higher levels compared with men, with a significant increase postmenopausal. In addition, obesity and diabetes are related with increased levels of PCSK9, while statins also increase PCSK9 expression. However, these parameters seem to determine only 23% of PCSK9 level variability.[16]

Atorvastatin 40 mg daily increased circulating PCSK9 by 34% after 16 weeks of treatment.[17] In addition, simvastatin 40 mg and the combination of simvastatin and ezetimibe 40/10 mg increased PCSK9 levels by 67.8% and 67.3%, respectively, while ezetimibe (10 mg/day) monotherapy was not related to a significant increase of PCSK9.[18] It seems that simvastatin's effect on PCSK9 levels is not enhanced by ezetimibe addition despite the extra decrease of LDL cholesterol. It was also found that a moderate reduction in serum LDL cholesterol (30–50% from baseline) results in a great increase of PCSK9 by even 120%.[18] Statins, by decreasing intracellular LDL cholesterol of the hepatic cell, enhance the activity of SREBP-2 (sterol regulatory element-binding protein-2), a transcription factor which activates the genes of both LDL receptor and PCSK9.[19] This mechanism is possibly responsible for the limited further statin efficacy as doses increase (the rule of 6), as LDL receptors and PCSK9 increase in parallel, leading to an increased LDL receptor degradation.

4. PCSK9 as a treating target

The key role of PCSK9 in LDL receptor catabolism and its relation to increased levels of LDL cholesterol, render its inhibition as a new treating target for LDL cholesterol reduction. Nature has already showed the way, as genetic defects associated with low or no PCSK9 activity are not related to any health problems[20] and markedly decrease CVD risk.[13]

PCSK9 can be inhibited in various ways using monoclonal antibodies (mAbs), oligonucleotides (antisense oligonucleotides), small sectors of silence RNA (siRNA) or small molecule inhibitors. Current research has mainly focused on monoclonal antibodies as PCSK9 inhibitors.[21]

Consequently, human monoclonal antibodies against PCSK9 protein have been developed and tested in animals first. Intravenous infusion of these antibodies resulted in a decrease of LDL cholesterol by 50%.[22,23] In humans, 3 monoclonal antibodies have been developed and tested, namely evolocumab (AMGEN), alirocumab (SANOFI-REGENERON) and bococizumab (PFIZER).

5. Clinical data (tables 1,2)

5.1. Effectiveness

During phase I clinical trials of evolocumab, 56 healthy persons (with baseline LDL cholesterol of 100–190 mg/dL) were randomized in a double blind trial, with the active treatment group receiving a single dose of 7–420 mg evolocumab (*iv* or *sc*). In comparison with the placebo, evolocumab decreased LDL cholesterol by

Table 1. Clinical studies with evolocumab.

Study	Patients	Background therapy	Treatment	Mean LDL-C reduction	Additional information
Phase I	56 healthy pts	None	Evolocumab (single dose 7–420 mg)	Up to 64%	
Phase I	57 dyslipidemic pts	Statin	Evolocumab (multiple doses)	Up to 81%	
MENDEL	406 pts with LDL-C between 100 and 190 mg/dL	None	Evolocumab (various doses)	Up to 50%	
LAPLACE-TIMI 57	631 pts with LDL >85 mg/dL	Statin±Ezetimibe	Evolocumab (various doses)	Up to 66%	
RUTHERFORD	167 pts with HeFH	Statin±Ezetimibe	Evolocumab (various doses)	Up to 55%	
GAUSS	160 statin intolerant pts	Low dose or no statin ±Ezetimibe	Evolocumab (various doses)	Up to 63%	ApoB –43%, Lp(a) –27%, TGs –10%, HDL-C +10.1%, ApoAI +10.6%
OSLER	1104 pts enrolled in phase II studies	Placebo in phase II	Evolocumab (420 mg every 4 weeks)	52.3%	
		Various doses of evolocumab in phase II	Evolocumab (420 mg every 4 weeks)	No significant changes (50.4% vs 52.1%)	
		Various doses of evolocumab in phase II	Placebo	Return to near baseline levels	
TESLA	8 pts with HoFH	Unknown	Evolocumab	16.5%	
GAUSS-2	307 statin intolerant pts	Placebo p.os.	Evolocumab (140 mg every 2 weeks or 420 mg once monthly)	53–56%	Additional reduction of LDL-C by 37-39% compared with ezetimibe monotherapy
LAPLACE-2	1899 dyslipidemic pts	Statin	Evolocumab (140 mg every 2 weeks or 420 mg once monthly) or Ezetimibe 10 mg daily	58-68% (additional reduction compared to ezetimibe)	
DESCARTES	901 dyslipidemic pts	Diet alone		55.7%	
		Diet plus atorvastatin 10 mg daily		61.6%	
		Diet plus atorvastatin 80 mg daily	Evolocumab (420 mg once monthly)	56.8%	
		Diet plus atorvastatin 80 mg plus ezetimibe 10 mg daily		48.5%	

LDL-C indicates low-density lipoprotein cholesterol, pts: patients, HeFH: heterozygous familial hypercholesterolemia, ApoB: apolipoprotein B, Lp(a): lipoprotein (a), TGs: triglycerides, HDL-C: high-density lipoprotein cholesterol, ApoAI: apolipoprotein AI, HoFH: homozygous familial hypercholesterolemia, p.os.: orally

Table 2. Clinical studies with alirocumab.

Study	Patients	Background therapy	Treatment	Mean LDL-C reduction	Additional information
Phase I	61 pts with dyslipidemia (familial or not)	None or atorvastatin	Alirocumab (50 mg every 2 weeks)	39.2%	
			Alirocumab (100 mg every 2 weeks)	53.7%	
			Alirocumab (150 mg every 2 weeks)	61%	
Phase II	77 pts with HeFH	Statin±Ezetimibe	Alirocumab (various doses)	28.9–67.9%	
Phase II	183 pts with LDL-C >100 mg/dL	Atorvastatin 10–40 mg daily	Alirocumab (various doses)	40–72%	
Phase II	92 pts with LDL-C >100 mg/dL	Atorvastatin 10 mg daily	Alirocumab plus atorvastatin 80 mg daily	73%	ApoB –58% Lp(a) –34% TGs –24% HDL-C +5.8% (maximum changes)
			Alirocumab plus atorvastatin 10 mg daily	66.2%	
			Placebo plus atorvastatin 80 mg daily	17.3%	
ODYSSEY FH I & II	735 pts with HeFH	Statin±Ezetimibe	Alirocumab (75–150 mg every 2 weeks)		Patients reaching specific LDL-C goals
				48.8% (FH I)	72.2%
				48.7% (FH III)	81.4%
ODYSSEY COMBO II	720 dyslipidemic pts	Statin (maximum tolerated dose)	Alirocumab (75–150 mg every 2 weeks) or Ezetimibe (10 mg daily)	50.6%	
ODYSSEY LONG TERM	2431 pts with high CV risk or HeFH	Statin (maximum tolerated dose)±other lipid-lowering treatment	Alirocumab (150 mg every 2 weeks)	61%	Patients reaching specific LDL-C goals: 81%

LDL-C indicates low-density lipoprotein cholesterol, pts: patients, ApoB: apolipoprotein B, Lp(a): lipoprotein (a), TGs: triglycerides, HDL-C: high-density lipoprotein cholesterol, HeFH: heterozygous familial hypercholesterolemia, CV: cardiovascular

64% (p<0.0001).[24] Next, 57 dyslipidemic patients (LDL cholesterol 70–220 mg/dL) on statins (low-medium or high dose) and FH heterozygotes (HeFH) were randomized to receive multiple doses of evolocumab. The maximum LDL cholesterol reduction observed in this study was 81% (p<0.001) compared with placebo.[24] In addition, significant and dose-related reductions were seen in total cholesterol, non-HDL cholesterol, ApoB and lipoprotein (a) [Lp(a)].[24]

In phase II clinical trials, 1364 patients were randomized to receive various doses of evolocumab. In the first study (MENDEL, n=406), LDL cholesterol was reduced up to 50% (p<0.0001 compared with placebo) in the drug monotherapy group.[25] In LAPLACE-TIMI 57 study (n=631), the combination of evolocumab with a statin (±ezetimibe) reduced LDL cholesterol by a maximum of 66% (p<0.0001) after 12 weeks.[26] In RUTHERFORD study in 167 HeFH patients on statins ± ezetimibe, LDL

cholesterol was decreased by 55% (p<0.001).[27] In the fourth study (GAUSS, n=160), LDL cholesterol reduction reached a maximum of 63% (p<0.001) in statin intolerant patients (receiving low dose or no statin therapy at all ± ezetimibe).[28] Tested doses were the 70 mg, 105 mg or 420 mg every 2 weeks and 280 mg, 350 mg or 420 mg every 4 weeks. In addition, significant reductions were seen in ApoB (43%), Lp(a) (27%) and triglycerides (10%), while HDL cholesterol and apolipoprotein AI were slightly raised (10.1% and 10.6%, respectively).[27] The choice of dose regimen will depend on patient wish to receive one injection of larger volume every month or one of smaller volume every 2 weeks.

The efficacy and safety of long term evolocumab use for 52 weeks were tested in the OSLER study. Eighty one percent of patients participating in phase II clinical trials were randomized again in a group receiving evolocumab+usual treatment (n=736) and a group receiving only usual treatment (n=368). Receiving evolocumab for the first time in OSLER study (patients in the placebo group in phase II) resulted in LDL cholesterol reductions by 52.3% (p<0.0001).[29] Patients who continued evolocumab treatment during this study (having been taking the drug in previous studies) kept their LDL cholesterol steadily low, while those who stopped evolocumab in OSLER study saw their LDL cholesterol levels return to baseline.[29]

TESLA is an important trial, being the only one to study the effectiveness of PCSK9 blockage in patients with homozygous FH (HoFH). In 8 patients with HoFH, evolocumab (420 mg every 4 weeks for at least 12 weeks) reduced LDL cholesterol by 16.5%. However, in 2 patients with total loss of LDL receptor activity, LDL cholesterol levels were not significantly reduced.[30]

Statin intolerant patients were enrolled in GAUSS-2 study and randomized in 4 groups, 2 receiving evolocumab 140 mg/2 weeks or 420 mg/4 weeks and placebo (*p.os.*) every day and 2 receiving placebo *sc* every 2 or 4 weeks and 10 mg ezetimibe (*p.os.*) daily. After 12 weeks, the 2 groups receiving evolocumab had 53–56% lower LDL cholesterol (compared with baseline), which stands for an additional 37–39% reduction compared with ezetimibe monotherapy.[31]

Patients with hypercholesterolemia or combined dyslipidemia treated with high doses of atorvastatin or rosuvastatin (±ezetimibe) participated in LAPLACE-2 study, receiving evolocumab 140 mg every 2 weeks or 420 mg every 4 weeks. After 12 weeks LDL cholesterol was additionally reduced by 58–68%.[32]

A phase III study named DESCARTES included 901 hypercholesterolemic patients with LDL cholesterol >75 mg/dL after 4 to 12 weeks of: (1) diet alone, (2) diet plus atorvastatin 10 mg daily or (3) 80 mg daily and (4) 80 mg atorvastatin plus 10 mg ezetimibe daily. These patients were randomly assigned in a 2:1 ratio to receive either evolocumab (420 mg) or placebo every 4 weeks. LDL cholesterol was reduced by 57% in the evolocumab group after 52 weeks. Depending on the background treatment, LDL cholesterol was reduced by 55.7% in the diet alone group, 61.6% and 56.8% in the atorvastatin 10 mg and 80 mg group, respectively and 48.5% in the atorvastatin 80 mg plus ezetimibe 10 mg group.[33]

Larger phase III studies have already began, with FOURIER study recruiting since early 2013. A total of 27,500 patients are about to be enrolled, all with a history of clinically evident CVD and LDL cholesterol above 70 mg/dL despite the best lipid lowering treatment (high dose statin±ezetimibe). The follow-up period will be 5 years and the primary endpoint will be the time to a new major CVD event (cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina or coronary revascularization), so that to test if additional reduction of LDL cholesterol leads to further reduction of CVD.

Sixty-one patients with hypercholesterolemia (familial or not), untreated or under atorvastatin, participated in a phase I clinical trial assessing alirocumab safety. No treatment discontinuation was reported due to adverse events. Among patients treated with atorvastatin, LDL cholesterol was reduced by 39.2%, 53.7% and 61% in the 50 mg, 100 mg and 150 mg bimonthly dose of alirocumab, respectively (p <0.001).[34]

In phase II clinical trials, LDL cholesterol was reduced by 28.9%–67.9% after various doses of alirocumab in 77 randomly allocated FH patients treated with statin ±ezetimibe. Another trial including 183 patients with LDL cholesterol >100 mg/dL despite treatment with atorvastatin (10–40 mg) showed LDL cholesterol reduction by 40–72% after 12 weeks of treatment.[35] In addition, 92 patients with LDL cholesterol >100 mg/dL treated with 10 mg atorvastatin daily were randomized in 3 groups. In the first group, receiving alirocumab and 80 mg atorvastatin, mean LDL cholesterol was reduced by 73.2%, while the combination of alirocumab with 10 mg atorvastatin in the second group reduced LDL cholesterol by 66.2%. The mean LDL cholesterol reduction was limited to 17.3% (p<0.001) in the third group, receiving placebo and 80 mg atorvastatin.[36]

The combination of atorvastatin and alirocumab reduced LDL cholesterol to <100 mg/dL in all patients and <70 mg/dL in more than 90% of the patients versus 52% and 17% of patients receiving placebo plus atorvastatin, respectively. ApoB, Lp(a) and triglycerides were reduced by a maximum of 58% (p <0.001), 34% (p<0.001) and 24% (p<0.03), respectively, and HDL cholesterol increased by up to 5.8% (p<0.005).[36]

The ODYSSEY program, including more than 10 phase III clinical trials of alirocumab, has already begun, with the expected participants exceeding 22,000. The most important trial is the ODYSSEY-OUTCOMES which assesses the effect of alirocumab on the time to a new CVD event (cardiovascular death, myocardial infarction, stroke, hospitalization due to unstable angina) in 18,000 patients older than 40 years with a recent (<52 weeks) hospitalization for an acute coronary syndrome and LDL cholesterol >70 mg/dL on high dose statin.

The ODYSSEY FH I & II trials were very recently presented. In 735 patients with heterozygous FH under treatment with statins ± ezetimibe, alirocumab further reduced LDL cholesterol by 48.8% (FH I) and 48.7% (FH II) compared with baseline. In addition, 72.2% (FH I) and 81.4% (FH II) of patients in the alirocumab group reached the goal for LDL cholesterol (<100 mg/dL for high risk patients and <70 mg/dL for very high risk patients).[37] In the ODYSSEY COMBO II trial (720 patients on maximum tolerated statin dose), LDL cholesterol was reduced by 50.6% after 24 weeks of treatment with alirocumab (compared with 20.7% reduction with ezetimibe, p<0.0001).[38]

The ODYSSEY LONG TERM trial is the largest phase III study for alirocumab with the longest follow-up period so far, including 2,431 patients with LDL cholesterol >70 mg/dL despite maximum tolerated statin dose±other lipid lowering treatment. By week 24, alirocumab was associated with mean LDL cholesterol reduction of 61% from baseline (whereas in the placebo group LDL cholesterol increased by 0.8%, p<0.0001). Furthermore, 76% of the patients receiving alirocumab saw their LDL cholesterol reduced at least in half from baseline (only 2% in the placebo group, p<0.0001), with no difference in the incidence of adverse events. A post-hoc analysis showed that the rate of major cardiovascular events (cardiac death, myocardial infarction, stroke, unstable angina requiring hospitalization) was lower in the alirocumab group compared with placebo (1.4 versus 3.0%, p<0.01).[39]

5.2. Safety

Evolocumab has been well tolerated. Total incidence of adverse events was comparable with the placebo, while no serious adverse events led to treatment discontinuation. In addition, no antibodies against the drug were detected. It is important that the drug shares no muscle-related adverse events with statins, as they were uncommon and similar in both treatment and placebo groups. Creatine kinase (CK) elevations were not common and liver enzymes increased very rarely.

Alirocumab can also be considered as a safe drug, taking into account that the treatment was not discontinued due to adverse events in any case. Moreover, the prevalence of any or muscle-related adverse event was similar between alirocumab and placebo (60% *vs* 61% and 5% *vs* 6% respectively).[36]

When monoclonal antibodies are injected local reactions at the injection site may occur (erythema, hematoma, hemorrhage, pain, and swelling). Reactions of this kind were observed with evolocumab. There were some considerations about the possible antibody-induced increase of hepatitis C virus infectivity. A possible mechanism of entry of the virus into the hepatic cell via LDL receptors and the drug-induced upregulation of LDL receptors could potentially increase virus penetration. However, statins also upregulate the expression of LDL receptors, but their wide use for decades did not result in a higher incidence of hepatitis C.

5. 3. Drug interactions

Monoclonal antibodies are eliminated by antigen-antibody complexes and phagocytosis and are not metabolized or excreted by the liver or kidneys. Thus, the activity of cytochrome P450 remains untouched, avoiding any interaction with statins or other drugs that use this metabolic pathway. Statin or any other drug pharmacokinetics are not affected by these new drugs.

6. Potential place in clinical practice

Monoclonal antibodies against PCSK9 can cover the treatment gap in: (1) statin intolerant patients, (2) patients with very high baseline LDL cholesterol (often attributed to FH), and (3) very high risk patients with low LDL cholesterol target, unachieved with current treatment.[37] Parenteral administration is a possible disadvantage of these drugs, although compliance may improve. Of course, the high cost, attributed to innovation and complicated production, is an important limitation.

7. Conclusion

All available data indicate that we stand before a new, revolutionary and safe treatment approach for the millions of dyslipidemic patients, promising effective CVD prevention. After a long time, we are able to further reduce LDL cholesterol beyond current levels, hoping to further decrease CVD events.

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