HORMONES 2016, 15(1):8-14

Expert Consensus

Expert consensus on the rational clinical use of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

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Received:04-12-2015, Accepted: 09-12-2015

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ABSTRACT

Two proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, evolocumab and alirocumab, have recently been approved by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of hypercholesterolemia. These fully human monoclonal antibodies selectively block PCSK9, thus permitting the low-density lipoprotein (LDL) receptor to effectively recycle to the surface of liver cells. The administration of these antibodies leads to robust LDL cholesterol (LDL-C) lowering by 50-60% on top of maximum hypolipidemic treatment. At least 4 randomized, placebo-controlled studies are under way and will address the question of whether the administration of these PCSK9 inhibitors is associated with a significant reduction of cardiovascular events. Because of the high cost associated with the use of these medications it is very important to consider which patients may gain the most benefit, at least until the results of outcome studies are available. In this Consensus paper, 34 clinicians/scientists define 3 groups of patients that should be currently considered as candidates for the use of these novel drugs. These include: 1a. Adults with established cardiovascular disease and LDL-C≥100 mg/dL while on lifestyle modifications and maximally tolerated hypolipidemic treatment, i.e. high-intensity statin + ezetimibe, 1b. Adults with diabetes and established cardiovascular disease or chronic kidney disease or target organ damage and LDL-C ≥100 mg/dL while on lifestyle modifications and maximally tolerated hypolipidemic treatment, i.e. high-intensity statin + ezetimibe, 2. Adults with familial hypercholesterolemia (FH) without established cardiovascular disease and LDL-C ≥130 mg/dL while on lifestyle modifications and maximally tolerated hypolipidemic treatment, i.e. high-intensity statin + ezetimibe (evolocumab is also indicated in children above 12 years with homozygous FH), and 3. Adults on high or very high cardiovascular risk who are statin intolerant and have an LDL-C ≥100 and ≥130 mg/dL, respectively, while on any tolerated hypolipidemic treatment.

Key words: Cardiovascular disease, Diabetes, Ezetimibe, Familial hypercholesterolemia, High-risk, LDL cholesterol, PCSK9, Statin intolerance, Statins

INTRODUCTION

Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays an important role in lipoprotein metabolism because it binds and accelerates the cellular degradation of low-density lipoprotein (LDL) receptors, thus preventing their recycling to the hepatocyte surface. This effect results in the increase of plasma LDL cholesterol (LDL-C) levels.[1-7]

The administration of fully human monoclonal antibodies that bind plasma PCSK9 of patients treated with statins (with or without ezetimibe) results in an additional reduction of LDL-C by 50-60% and the achievement of lipid-lowering therapy goals in the vast majority of high-risk patients.[7-19] Clinical and experimental data have shown that statins, as opposed to their ability to reduce LDL-C levels, increase

PCSK9 levels.[1] This increase is due to the activation of the Sterol Regulatory Element-Binding-Protein-2 (SREBP-2), a transcription factor that induces gene expression and therefore increases the levels of LDL receptors as well as of PCSK9.[1] These findings reinforce the clinical trial data showing that inhibition of PCSK9 with monoclonal antibodies enhances the lipid-lowering effect of statins. Moreover, it has been shown that PCSK9 inhibitors decrease levels of lipoprotein (a) [Lp(a)] by approximately 25%, triglycerides by 9%, non-high density lipoprotein (HDL) cholesterol by 52% and apolipoprotein B by 43% as well as increase HDL cholesterol (HDL-C) levels by 9% and apolipoprotein AI by 5%.[8-20]

Three large meta-analyses of PCSK9 inhibitors, evolocumab and alirocumab (meta-analysis of 24 randomized studies by Navarese et al, 25 randomized studies by Zhang et al and 17 randomized studies by Lipinski et al), confirmed the efficacy and safety of both drugs, without differences regarding serious adverse events among patients treated with evolocumab or alirocumab and placebo.[8-10] Of note, injection-site reactions and neurocognitive adverse events were more frequent in patients on PCSK9 inhibitors compared with placebo.[10] The possible association of PCSK9 inhibitors with neurocognitive adverse events is under scrutiny in ongoing studies.

It is of particular interest that two studies recently published (ODYSSEY LONG TERM & OSLER studies) showed that administration of both drugs, apart from the well tolerated reduction in LDL-C, resulted in a significant (50%) reduction in cardiovascular (CV) events (treatment duration 1 year, starting LDL-C levels of ~120 mg/dL).[19,20] However, these studies were not designed to evaluate the effect of the drugs on CV events, while the number of CV events recorded during treatment was low and the time of prospective follow-up of patients was limited. Ongoing studies will answer the question whether the reduction of LDL-C through PCSK9 inhibition leads to a proportional reduction of CV events in cases of long-term administration, without adverse events.

Regulatory authorities in the USA and Europe [Food and Drug Administration (FDA) and European Medicines Agency (EMA)] have approved the administration of these drugs to adult patients with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia, as adjunct treatment to diet:

- In combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or,
- Alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant or for whom a statin is contraindicated.

Evolocumab has received an additional indication in adolescents over 12 years old with homozygous familial hypercholesterolemia (FH) in combination with other lipid-lowering treatments.

The drugs are administered as subcutaneous injections every 2 weeks (evolocumab 140 mg and alirocumab 75 or 150 mg) or 4 weeks (evolocumab 420 mg).

Patients who could benefit from treatment with PCSK9 inhibitors

Until the announcement-publication of the prospective randomized clinical trials that will confirm the effect of these drugs on CV morbidity and mortality, *it is proposed that their prescription be limited to specific patient groups at very high risk who are expected to benefit from the treatment.*

The following guidelines are consistent with the recent recommendations of the US National Lipid Association (NLA) and are summarized in Table 1.[11] It is to be noted that patient adherence with already administered lipid-lowering therapy should always be examined first. The patient groups that are expected to benefit from treatment are: (1) patients with FH, (2) patients with established vascular disease and very high-risk diabetic patients who do not achieve the hypolipidemic treatment goals with the maximum available lipid-lowering therapy (high doses of effective statins + ezetimibe), and (3) patients intolerant to statins. Patients with FH are at high CV risk because of very high levels of LDL-C. These patients often do not achieve the goals of hypolipidemic treatment in daily clinical practice. It must be underlined that a percentage of patients display intolerance to statins, i.e. myalgia with or without an increase in muscle enzymes, which makes it difficult to continue treat-

Table 1. Profiles of eligible patients for administration of monoclonal antibodies against PCSK9 until the completion of large randomized clinical trials with cardiovascular outcomes

Group of high- to very high-risk individuals		Ultimate treatment goal
1a. Adult patients with established atherosclerotic CV disease (coronary, carotid or peripheral vessels) and LDL-C ≥100 mg/dL 1b. Diabetic patients with: known CV disease or chronic kidney disease (estimated glomerular filtration rate ≤60 mL/min/1.73 m2 and/or albuminuria for at least 3 months) or other target organ damage and LDL-C ≥100 mg/dL	Under appropriate health-diet and pharmaceutical treatment with the maximum tolerated dose of effective statin (atorvastatin 40/80 mg or rosuvastatin 20/40 mg) + ezetimibe 10 mg	LDL-C<70 mg/dL
2. Adult patients FH without known atherosclerotic cardiovascular disease and LDL-C ≥130 mg/dL*	Under treatment with the maximum tolerated dose of effective statin (atorvastatin 40/80 mg or rosuvastatin 20/40 mg) + ezetimibe 10 mg	LDL-C <100 mg/dL
3. High- or very high-risk patients (HELLENIC SCORE >5% or >10%, respectively) who are intolerant to statins and have LDL-C ≥130 or ≥100 mg/dL, respectively	Under any tolerated lipid-lowering treatment	LDL-C <70 mg/dL in very high-risk patients LDL-C <100 mg/dL in high-risk patients

* Evolocumab has received additional indication in adolescents over 12 years old with homozygous FH in combination with other lipid-lowering treatments.

Table 2. Dutch Lipid Clinic Network diagnostic criteria for Familial Hypercholesterolemia

Criteria		Score
Family history	First degree relative with:	
	• Known premature coronary or vascular disease (men aged <55 years, women aged <60 years)	1
	• LDL-C above the 95th percentile for age and gender	1
	• Tendinous xanthomata and/or corneal arcus	2
	First degree relative <18 years with LDL-C above the 95th percentile for age and gender	2
Clinical history	Patients with premature coronary artery disease (men aged <55 years, women aged <60 years)	2
	Patients with premature peripheral arterial disease or ischemic stroke (men aged <55 years, women aged <60 years)	1
Physical examination	Tendinous xanthomata	6
	Corneal arcus prior to age 45 years	4
Laboratory check	LDL-C, mg/dL (mmol/L)	
	• ≥330 (≥8.5)	8
	• 250-329 (6.5-8.4)	5
	• 190-249 (5.0-6.4)	3
	• 155-189 (4.0-4.9)	1
DNA analysis	Functional mutation in the LDL receptor, apolipoprotein B or PCSK9 gene	8
Total score	Diagnosis	
>8	Definite FH	
6-8	Probable FH	
3-5	Possible FH	

ment with statins or to administer high doses of these drugs.[21-25]

Diagnosis of FH

The diagnosis of heterozygous FH is set clinically using the Dutch criteria (Table 2 and FH score in

App Store (https://appsto.re/gr/wF4Q7.i), FH score in Google Store (https://play.google.com/store/apps/details ?id=com.ajjumax.helleniccalculat) and Download in desktop (http://web.alphabit.gr/FHCalculator/index.html) and when the patient has a score ≥6 (probable or definite FH).[26-38]

The Hellenic Atherosclerosis Society has already initiated a nationwide registry of patients with FH (HELLAS FH Registry - Hellenic Registry of Patients with FH). The inclusion of any patient in this registry also confirms its diagnosis.

Diagnosis of statin intolerance

The diagnosis of statin intolerance is set in patients who: (a) display significant increases in creatine kinase (CK) >5 times of the upper limit reference values, and/or, (b) irrespective of any increase in CK, display muscle symptoms which may be attributed to statins (pain, fatigue, weakness, cramps) and after the exclusion of any other factors which could cause similar symptoms (Table 3) and/or any possible interactions of the co-administered drugs have been excluded (Table 4).

In order to confirm possible statin intolerance, a sequential administration of at least 2 different statins starting at low doses followed by a careful dosage up-titration over a few weeks is required (Table 5). The improvement of symptoms following statin treatment discontinuation and their reappearance with the re-administration of the same or a different statin reinforce the diagnosis of statin intolerance. The therapeutic options in patients intolerant to statins before administration of the PCSK9 inhibitors are shown in Table 6.[21-25]

Table 3. Causes to be excluded in patients with muscular pains and/or CK increase before these findings are attributed to statins.

1. Exercise-Muscle strain
2. Intramuscular injections
3. Drugs (cocaine, heroin, amphetamines) - Alcohol
4. Hypothyroidism
5. Infections
6. Electrolyte disorders (e.g. hypokalemia)
7. Metabolic myopathies
8. Inflammatory and autoimmune myositis

Table 4. Drug interactions of statins

1. Fibrates (mainly gemfibrozil - not fenofibrate)
2. Coumarin anticoagulants
3. Cyclosporine
4. Erythromycin and other macrolides (clarithromycin)
5. Itraconazole and other antifungal medicines
6. Antidepressants (nefazodone)
7. Protease inhibitors
8. Dihydropyridines, as well as diltiazem/verapamil (mainly with simvastatin)
9. Amiodarone (mainly with simvastatin/lovastatin)
10. Grapefruit juice
11. Drugs that induce the activity of CYP3A4 (phenytoin, rifampicin)

Table 5. Statins marketed in Greece (approved dose range)

Statin	Dose range
Atorvastatin	10–80 mg
Lovastatin	20–80 mg
Pitavastatin	1–4 mg
Pravastatin	10–40 mg
Rosuvastatin	5–40 mg
Simvastatin	10–40 mg
Fluvastatin	20–80 mg

Table 6. Therapeutic options in patients intolerant to statins prior to the administration of PCSK9 inhibitors.

1. Aggressive health-diet changes.
2. Administration of ezetimibe (10 mg/day).
3. Administration of a combination of ezetimibe (10 mg/day) with colesevelam (3.75 g/day). The expected reduction in LDL-C is 30%. Alternatively, a combination of ezetimibe with fenofibrate may be administered.
4. Potential careful administration of pravastatin 20 mg/day or fluvastatin 40 mg/day.
5. Administration of rosuvastatin 5 mg or atorvastatin 10 mg every other day or twice per week or once per week, in combination with daily ezetimibe.
6. Measurement of vitamin 25(OH)D3 levels and supplementation in cases of reduced levels, although the evidence is limited.
7. Dealing with the factors listed in Table 3.

FINANCIAL AND COMPETING INTEREST DISCLOSURE

This consensus was written independently and

was not financed by the pharmaceutical industry. Some authors have given lectures and participated in congresses and advisory boards of various pharmaceutical companies; however, they have no conflict of interest in terms of employment, stock ownership or options, grants, or patents received or pending, or royalties. No writing assistance was utilized in the production of this consensus.

ACKNOWLEDGEMENT

This consensus was published in Greek in the Hellenic Journal of Atherosclerosis (Hellenic J Atheroscler 2015; 6(Suppl): 3-8). After agreement of the two Editors-in-Chief it is published in English in an extended form in Hormones.

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