Chapter

Utility and Appropriate Use of PCSK9 Inhibitors in the Current Era

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Abstract

Atherosclerotic cardiovascular diseases (ASCVD) remain the number one cause of death and morbidity in the country. Elevated cholesterol/hyperlipidemia has been considered one of the major risk factors for ASCVD. Statins have been the main stay therapy for treating hyperlipidemia achieving remarkable clinical benefits; however; its inability to achieve the desired reduction in the low density lipoprotein cholesterol (LDL) in some people and the disabling side effects from it in others, has led to a search for an alternative therapy. One of the groundbreaking inventions in this field has been the advent of the proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i). These agents have similar efficacy to high intensity statins and at the same time are tolerated well with a low incidence of side effects. Based on the results from multiple large scale clinical outcome trials, this class of LDL-C lowering agents has been recommended as appropriate second-line agents, or as an alternative therapy in cases of significant statin intolerance, for patients with established ASCVD and suboptimal LDL levels. As evidence supporting their efficacy and safety continues to mount, use of PCSK9i is likely to keep expanding in the current ASCVD population. In this chapter we discuss the advent of PCSK9i, their clinical utility, and their appropriate use keeping in view the high drug cost and other barriers in prescribing them.

Keywords: proprotein convertase subtilisin/kexin type 9 (PCSK9i), hyperlipidemia, ASCVD, LDL-C, statins, evolocumab, alirocumab

1. Introduction

Hyperlipidemia is a well-known and established cardiovascular risk factor, with a global prevalence of approximately 39% per a World Health Organization report from 2011 [1]. Cholesterol lowering therapy, specifically low-density lipoprotein (LDL) lowering therapy, has been shown to significantly reduce the prevalence of atherosclerotic cardiovascular disease (ASCVD). The management of hyperlipidemia has evolved greatly over the last thirty years. Since the development of commercially available statins in the 1980's, this class of medication has become the hallmark for treatment of hyperlipidemia, with multiple adjunct therapies emerging over the past decade. And while statins are substantially efficacious in lowering LDL-C, a portion of patients are not able to achieve their goal LDL-C on statins alone. Another subset of patients develop statin induced side effects which either

limits up titration of statin therapy, or in some patients, even prevents the use of a small dose of statins. In order to obtain optimal ASCVD risk reduction, further lowering the LDL-C has been achieved with the use of ezetimibe, as well as the use of proprotein convertase subtilisin/kexin type 9-inhibitors (PCSK9i).

The PCSK9i: evolocumab and alirocumab, have shown promising results over the last several years, not only in major randomized landmark trials but also in clinical practice. These agents are one of the most efficacious antihyperlipidemic therapies and have shown to achieve a reduction in low density lipoprotein (LDL) by 50–65% [2, 3]. Two large outcomes trials [4, 5] have demonstrated that both evolocumab and alirocumab are effective in reducing major adverse cardiac events in high risk atherosclerotic cardiovascular disease (ASCVD) conditions. Most recent multi-society guidelines are endorsing the use of PCSK9i in patients at very high cardiovascular risk [6], which includes patients with familial hypercholesterolemia. A joint consensus statement from the European Society of Cardiology and European Atherosclerosis Society suggested that PCSK9i could be considered in patients with clinical ASCVD treated with maximal tolerated statin therapy and/or ezetimibe who have continued to have LDL-C > 100 mg/dL [7]. Despite all the available data supporting its efficacy and clinical benefits, the cost-effectiveness and economic value of PCSK9 inhibitors has been reported to be 'low value' as measured in quality adjusted age years. [6]. The guidelines have also felt that the economic value of PCSK9i would be improved by restricting its use to patients at high risk of ASCVD events, specifically initiating PCSK9i in high risk patients with LDL-C values >120, despite optimal lipid lowering therapy. In this article we describe the clinical use of PCSK9i in the current era and its appropriate use.

2. Mechanism of action

The proprotein convertase subtilisin/kexin-9 (PCSK9) is a serine protease, which has been found to be integral in the regulation of LDL-C plasma concentrations. The LDL receptors (LDL-R) present on hepatocytes are responsible for binding circulating LDL-C and removing them from plasma. In the absence of PCKS9, the LDL-C/LDL-R complex enters hepatocytes within the endosome and dissociates into LDL-C and LDL-R as a result of the acidic pH present in the endosome. The LDL-R is then recycled back to the hepatocyte surface, making it available to bind more LDL-C, thereby lowering the serum LDL-C concentration. In the presence of PCSK9, however, the LDL-C/LDL-R complex does not dissociate within the endosome, and the entire complex is marked for lysosomal degradation. Without LDL-R recycling, less LDL-C is removed from circulation, resulting in higher LDL-C plasma concentrations [8].

The clinical implications of PCSK9 have been demonstrated in both loss of function and gain of function mutations. A gain of function mutation was first discovered in two French families with familial hypercholesterolemia that was not associated with LDLR or APOB mutations [9]. The mutated allele created an overexpression of PCSK9, and subsequently elevated plasma LDL-C levels, with sequelae of significant hypercholesterolemia including tendinous xanthomas and risk of premature ASCVD in the fourth and fifth decade. While gain of mutation functions have been discovered in other cohorts in Utah, Norway and the United Kingdom, familial hypercholesterolemia secondary to PCKS9 gain of function mutations is uniquely rare [8]. However, this discovery provided insight to PCSK9 activity, and that overexpression of this protein results in excessive LDL-C in vivo. This discovery also provided the third locus for autosomal dominant familial

hypercholesterolemia inheritance, adding to the already known LDL-R and APOB mutations [9].

Conversely, loss of function mutations of PCKS9 have been shown to significantly reduce circulating LDL levels, which sparked interest in accumulating data on how this translated to reduced ASCVD risk. One study discovered that loss of function mutations in one population was present in 2.3% of black patients, and 3.2% of white patients. The loss of PCKS9 function resulted in a 28 percent mean reduction of LDL, and an 88 percent reduction in ASCVD risk in the black population, and a 15 percent mean reduction in LDL and a 47 percent reduction in ASCVD risk in the white populations [10]. This review also supported the idea that loss of PCSK9 function would not impact viability, as both populations in this review had intact reproductive or neurologic function. This was further corroborated in PSCK9 knockout mice, in which no PCKS9 function resulted in exceedingly low LDL-C levels [11, 12]. These findings suggest that PCKS9 function is not vital for life, and complete inhibition of this proteinase would be well tolerated in humans, further sparking the search to create a mechanism in which we could inhibit PCKS9 function pharmaceutically.

Currently, two monoclonal against PCSK9 are available: alirocumab and evolocumab, which bind with a 1: 1 ratio to circulating PCSK9. Once the antibody binds to PCSK9, PCSK9 is unable to attach to LDL receptors which in turn inhibits the receptors' degradation. This leads to an increased expression of LDL receptors on hepatocytes, leading subsequently to rapid clearance of LDL particles [13].

3. Approved indication

The Food and Drug Administration (FDA) has approved alirocumab and evolocumab as "an adjunct to diet and maximally tolerated statin therapy for treatment of adults with heterozygous Familial Hypercholesterolemia (FH) or clinical ASCVD who require additional lowering of LDL-C." Evolocumab is also indicated for treatment of homozygous FH and, based on the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) trial, "to reduce the risk of myocardial infarction (MI), stroke, and coronary revascularization in adults with established CVD."

4. Dosing and adverse effects

Alirocumab in the doses of either 75 mg or 150 mg could either be given subcutaneously every 2 weeks, or as a monthly 300 mg subcutaneous injection. LCL-C levels decrease around 45% from the 75 mg dose, and LCL-C levels decrease approximately 55–60% with the 150 mg dose.

Evolocumab also could be either given in a dose of 140 mg subcutaneous injections every 2 weeks, or as a 420 mg subcutaneous injection monthly. Both doses lower LDL-C approximately 55–60%. Besides lowering LDL, both alirocumab and evolocumab achieve mild lowering of triglycerides by 10–15% range. A modest increase in HDL cholesterol by 5–10% has been noted as well.

5. Adverse reactions

Trials involving PCKS9 inhibitors have included patients that were both tolerant and intolerant to statin therapy, providing information on their safety profile.

Serious adverse reactions attributed directly to drug injection have been rarely reported, with <10% of patients requiring drug discontinuation during separate study trials [14, 15].

With both available PCKS9i injectable solutions, the most reported adverse effect has been injection site reaction, which occurs in approximately >5% of patients, including injection site allergic reactions. Additional adverse reactions that have been reported by both study data and real-world use databases include upper respiratory infections, nasopharyngitis, myalgias, back pain and neurocognitive events including memory impairment and confusion [14, 15].

In regard to myalgia and muscle symptoms, evolocumab was studied head to head against ezetimibe in the GAUSS-3 trial [14]. This trial examined patient who were intolerant to statins due to muscle symptoms, and randomly assigned patients to either evolocumab or ezetimibe. In this trial population, drug discontinuation due to muscle symptoms occurred in 6.8% of ezetimibe patients and 0.7% of evolocumab patients. However, more patients in the evolucumab arm, 2.8% had elevations in CK levels, compared to 1.4% of patients in the ezetimibe arm.

The only absolute contraindication to PCKS9 inhibitor use is a history of hypersensitivity reaction to prior PCKS9 injections, with limited data available to determine whether allergenic cross-reactivity exists between the two available PCKS9 formulations.

6. Available scientific evidence

The FOURIER trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) tested clinical outcomes when evolocumab was added to maximum statin therapy in ASCVD patients [16]. A total of 27,564 patients were randomized to either evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or placebo. Patients who were treated with evolocumab had close to 60% LCL-C lowering. After a follow up period of 24 months, the combined endpoint of cardiovascular mortality, myocardial infarction, stroke, hospitalization related to angina, or revascularization was seen in 9.8% of patients in the evolocumab group compared to 11.3% in the placebo group.

The ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) evaluated outcomes in patients treated with alirocumab after acute coronary syndrome who were already on maximally tolerated statins [17]. A total of 18,924 patients were randomized to either alirocumab or placebo. The composite endpoint of CV death, nonfatal myocardial infarction, fatal and nonfatal stroke, or hospitalization due to angina occurred less the alirocumab arm compared to placebo (9.5% Vs. 11.1%, $p = 0.003$).

The GLAGOV (Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound) trial was designed to study the effect of using PCSK9 inhibition on atherosclerotic plaque burden and regression [18]. Over a period of 18 months a total of 968 patients with ASCVD were treated with either evolocumab or placebo. LDL-C levels were significantly lower in the evolocumab group compared to the placebo group. Atheroma volume was assessed using intravascular ultrasound, which demonstrated larger reduction in the evolocumab group compared to placebo.

The ODYSSEY ALTERNATIVE trial assessed the performance of alirocumab against ezetimibe and atorvastatin in patients with statin associated skeletal muscle effects [19]. Patients were randomized in a 2:2:1 fashion to either alirocumab 75 mg subcutaneously Q2W, ezetimibe 10 mg daily, or atorvastatin 20 mg daily.

Alirocumab significantly reduced LDL-C at 24 weeks compared with ezetimibe; % decrease was 45% vs. 14.6%, difference 30.4, $p < 0.0001$. Muscle-related side effects were lower in the alirocumab arm (32.5%) compared with the ezetimibe (41.1%, $p = 0.096$) and atorvastatin arms (46%, $p = 0.042$). Alirocumab was found to be superior to ezetimibe in lowering LDL-C levels and achieving target levels in patients with statin intolerance, with a lower risk of muscle-related side effects.

The GAUSS-2 (Global Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects-2) trial assessed primarily the safety of evolocumab in patients with statin-associated muscle side effects [20]. It was a double-blind study in which patients were randomized to either evolocumab or ezetimibe. Superior efficacy and no muscle-related adverse events requiring discontinuation was seen in patients treated with evolocumab.

7. Appropriate use

Based on the results from multiple large scale clinical outcome trials of PCSK9i, this class of LDL-C lowering agents has been recommended as appropriate second-line agents, or as an alternative therapy in cases of significant statin intolerance, for patients with established ASCVD and suboptimal LDL levels. As evidence supporting their efficacy and safety continues to mount, use of PCSK9i is likely to keep expanding in the current ASCVD population.

The ACC/AHA multi-society Cholesterol Clinical Practical Guidelines released in late 2018 give a class I recommendation for PSCK9i in patients with clinical ASCVD and very high risk (VHR) for future ASCVD events who are on maximally tolerated statin therapy and ezetimibe [6]. There is also a class IIa recommendation for VHR patients with ASCVD taking maximally tolerated statin therapy and ezetimibe with LDL-C ≥ 70 mg/dL (≥1.8 mmol/L) or a non-HDL-C level ≥ 100 mg/dL (≥2.6 mmol/L) to consider PCSK9i. Criteria to be considered VHR include major ASCVD events such as acute coronary syndrome within the past 12 months, history of myocardial infarction, history of embolic stroke, and symptomatic peripheral arterial disease, as well as high-risk conditions such as age ≥ 65 years old, heterozygous familial hypercholesterolemia, history of primary coronary artery bypass surgery or percutaneous coronary intervention, diabetes mellitus, hypertension, chronic kidney disease stage III or worse, ongoing tobacco use, persistent elevated LDL-C ≥ 100 mg/dL (≥2.6 mmol/L) despite maximally tolerated statin therapy and ezetimibe, and history of congestive heart failure. Regarding primary prevention, patients with heterozygous familial hypercholesterolemia aged 30 to 75 years old with an LDL-C ≥ 100 mg/dL (≥2.6 mmol/L) while taking maximally tolerated statin and ezetimibe therapy and patients aged 40 to 75 years old with a baseline LDL-C ≥ 220 mg/dL (≥5.7 mmol/L) and have an on-treatment LDL-C ≥ 130 mg/dL (≥3.4 mmol/L) while taking maximally tolerated statin and ezetimibe, the addition of a PCSK9i is given a class IIb recommendation.

Despite strong multi-societal recommendations, uptake rates for PCSK9i have lagged. A study looked at electronic health record data to characterize use of PCSK9i, in addition to standard therapies [21]. Data were obtained from 18 health systems within the National Patient-Centered Clinical Research Network using a common data model. Out of more than 17.5 million adults, 3.6 million met study criteria. Approximately half of patients had been prescribed lipid-lowering medication but <1% were prescribed PCSK9i. A trend towards increased PCSK9i prescription over time was seen for patients with ASCVD but not for those with dyslipidemia. PCSK9i, which effectively lower LDL cholesterol, had low use during this surveillance period.

Cost, or perceived expense, has been another barrier limiting patient access to PCSK9i use. High co-pays have been shown to lower access to PCSK9i, despite Medicare and other third-party payer coverage for PCSK9i [22]. Cost-effective analyses are essential in navigating which scenarios are prudent for treatment. Prior to October 2018, most cost-effectiveness studies concluded that PCSK9i were not cost-effective with the accepted threshold of $100,000 per quality-adjusted life-year (QALY) gained and cost of treatment estimated around $14,000 a year [23, 24]. However, in October 2018, the list price of evolocumab was decreased by 60% to $5850 in the United States, in an effort to lower copays and improve patient access. This dropped the ratios below the threshold of $50,000 per QALY gained and meeting accepted cost-effectiveness benchmarks [25]. Reducing cost can improve access to PCSK9i, however, prior authorization requirements, lack of insurance approval, and unfamiliarity amongst healthcare providers with this relatively new class of drug remain problematic.

8. Conclusion

PCSK9i have emerged as a breakthrough antihyperlipidemic therapy in the current era, where ASCVD is the leading cause for morbidity and mortality. PCSK9i are efficacious and safe. Current literature on their suboptimal use in real-world settings indicates that a large proportion of these patients could benefit from more aggressive treatment with this class of lipid lowering therapy. The cost-effectiveness of PCSK9i can be improved by restricting its use in patients with increased risk of ASCVD, who derived more benefit in the PCSK9i outcome trials. Also, the most recent AHA/ACC multi-society guidelines on the management of hyperlipidemia gave a class 1 recommendation to adding ezetimibe to maximally tolerated statin therapy for secondary prevention prior to initiation of PCSK9 inhibitors. This would also help triage PCSK9i use in people who are highest risk which in turn would improve its cost effectiveness.

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