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PCSK9 Inhibitors: A Review of the Efficacy, Safety and Current Literature Recommendations

Lacey L. Jandrin
University of North Dakota

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Abstract
Atherosclerotic cardiovascular disease is the leading cause of morbidity and mortality in developed countries. It is estimated that 60 million Americans have LDL-C levels > 160 mg/dl. Only about 1/3 of these patients meet LDL treatment goals of < 70 mg/dl indicating a need for greater control. High dose statins have been the mainstay in the treatment of dyslipidemia. However, up to 20% of patients are still intolerant of statins indicating a need for secondary treatment strategies. This lead to the development of monoclonal antibodies to proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. PCSK9 inhibitors result in decreased destruction of the low-density lipoprotein receptor (LDL-R) which leads to an increase in the transport of LDL-C to its destruction reducing LDL-C levels in the blood. The purpose of this study is to analyze the literature available on the efficacy and safety of new PCSK9 inhibitors. The results of this literature review indicated that PCSK9 inhibitors effectively lowered LDL-C by an average of approximately 50%. The evidence reviewed by this analysis indicates that 70% of patients treated with PCSK9 inhibitors met LDL-C goals. The findings also indicate that the side effects associated with this new class of medications are comparable to current side effects seen with traditional cholesterol lowering agents. The largest side effect seen in up to 10% of patients were injection site reactions and did not require discontinuation of the medication. The results of this analysis indicate that PCSK9 inhibitors may be of benefit in patients who are statin intolerant, do not meet LDL-C goals on traditional statin therapy or have familial hypercholesterolemia. Education in use of injectables, cost and insurance coverage and dosing schedule are likely to be areas of continued research and may affect the use of this new class of cholesterol lowering agents.

Introduction
- Elevated levels of low-density lipoprotein cholesterol (LDL-C), have been implicated in increased risk of major cardiovascular events making the reduction of LDL-C a major goal in the reduction of atherosclerotic cardiovascular disease.

Statement of the Problem
- Even with high dose statin therapy, only one-third of patients reach goal LDL-C levels <70 mg/dl.
- Approximately 10-20% of patients are unable to tolerate statins due to significant muscle related adverse reactions.
- The main agent utilized in patients who are statin intolerant is ezetimibe, which at its maximum, has the ability to lower cholesterol by 18% (Sullivan, 2012) leaving many patients with LDL-C levels > 160 mg/dl.
- This has led to the development of a new class of therapeutics, the proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9 inhibitors).
- Current Phase 3-1 trials are investigating the pathophysiology, efficacy, side effects, dosing and areas for future research of this new class of cholesterol lowering agents.

Discussion
- Ballantyne, Sullivan, Koren, Raab, Robinson, Stros and Roth have all demonstrated the ability of the PCSK9 inhibitors to effectively lower cholesterol levels and LDL-C levels by 27-63%.
- The ability to demonstrate long term cardiovascular risk reduction has yet to be fully investigated due to the fact that long term post hoc analysis has yet to be completed. Initial results from one study conducted by Robinson et al did demonstrate a 48% reduction in cardiovascular events in the study group versus the control.
- It appears that patients that are statin intolerant due to myalgias would be able to transition to PCSK9 inhibitor therapy without increased risk of addition myalgias.
- Due to patient inexperience with injectable agents, it will be imperative that providers provide an option for education to allow patients to become comfortable and trained in the use of injectable agents in order to decrease injection site reactions.

Applicability to Clinical Practice
- Research has demonstrated that PCSK9 inhibitors are highly efficacious in decreasing serum cholesterol levels demonstrating the ability to decrease cholesterol levels up to 50%.
- Authors indicate that the dose selection will likely be left to the clinician. The benefit of selecting a high dose and titrating down lies in the ability to quickly decrease cholesterol thereby decreasing risk of cardiovascular disease.
- Ballantyne and Roth are in agreement that bi-monthly dosing may be the most appropriate regimen as it results in a very steady state of control of cholesterol versus the variability seen with monthly dosing schedule.
- Given the consistent ability of the PCSK9 inhibitors to significantly decrease LDL-C levels, it appears that this new class of therapeutics will present an option for patients and clinicians to better decrease significant cardiovascular disease risk.
- It does not appear that PCSK9 inhibitors would be marketed nor expected to replace traditional statin therapy at this time, however they will likely present an option to clinicians who have patients who are intolerant to statins, not adequately controlled on max dose therapy, or who present with familial hypercholesterolemia.

Research Question
In patients with hyperlipidemia that is not well controlled with traditional statin therapy, do PCSK9 inhibitors bring LDL cholesterol closer to goal than placebo?

In Patients Treated with PCSK9 Inhibitors, are Side Effects More Severe than Traditional Statin Therapy, Ezetimibe or Placebo?

What Does Current Literature Say About Dosing and Future Research?

References