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

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Abstract

Atherosclerotic cardiovascular disease is the leading cause of morbidity and mortality in developed counties. It is estimated that 60 million Americans have LDL-C levels > 160 mg/dl. Only about 1/3 of these patients meet treated LDL cholesterol goals of < 70 mg/dl indicating a need for greater control. High dose statins have been the mainstay in treatment of dyslipidemia, however, up to 20% of patients are statin intolerant 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 effectively 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 indicate 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 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 struggling with elevated cholesterol levels and therefore increased risk for cardiovascular events.
- This has led to the development of a new class of therapeutics, the proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9 inhibitors).
- Current Phase 1-3 trials are investigating the pathophysiology, efficacy, side effects, dosing and areas for future research of this new class of cholesterol lowering agents.

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?

Literature Review

- The goal of the PCSK9 inhibitors is to decrease the amount of PCSK9 that is available to bind to the LDL-R allowing the LDL-R to bind to and eliminate more LDL-C, effectively decreasing the level of serum LDL-C.
- Ballantyne et al demonstrated a decrease in total cholesterol of 27.6-53.4 mg/dl, a 27-53% reduction from baseline when assessing efficacy in bi-monthly and monthly injections of PCSK9 inhibitors.
- Sullivan et al demonstrated a 41-63% decrease in LDL-C treated with PCSK9 inhibitors compared to a 15% decrease in those treated with Ezetimibe.
- Raal et al looked at the effect of PCSK9 inhibitors in group treated at bi-monthly and monthly intervals. They showed a 59.2% reduction in LDL-C in the bi-monthly group and a 61.3% reduction in the group treated monthly.
- In a study by Robinson et al, a 61.0% reduction in LDL-C was demonstrated in the PCSK9 inhibitor group compared to a 0.8% increase in LDL-C in the placebo group.
- Koren et al showed that 70% of patients in the PCSK9 inhibitors group met their LDL-C goal compared to only 1% of the placebo group and 2% of the ezetimibe group
- Stroes and Roth also demonstrated significant reductions in LDL-C, with the majority of patients meeting their LDL-C goals.
- Ballantyne, indicated that the most prevalent side effect noted by patients treated with PCSK9 inhibitors was injection site reactions ranging in prevalence from 4-10% of patients.
- Additional side effects reported in a small percentage of patients included nasopharyngitis, fatigue, nausea, diarrhea and myalgias.

Discussion

- Ballantyne, Sullivan, Koren, Raal, 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 specific to their target, do not penetrate the blood brain barrier, have a long serum half-life, and limited adverse side effects making them a solid choice in the treatment of high cholesterol.
- Research shows that PCSK9 inhibitors are highly efficacious in decreasing serum cholesterol levels demonstrating the ability to decrease cholesterol levels by upwards of 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.

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