5-4-2016

PCSK9 Monoclonal Antibodies: Promising New Pharmacologic Therapy for the Treatment of Hyperlipidemia

Courtney Feil

PCSK9 Monoclonal Antibodies:

Promising New Pharmacologic Therapy for the Treatment of Hyperlipidemia

Courtney N. Feil

University of North Dakota

PERMISSION

Title: PCSK9 Monoclonal Antibodies: Promising New Pharmacologic Therapy for the Treatment of Hyperlipidemia

Department: Nursing

Degree: Master of Science

In presenting this independent study in partial fulfillment of the requirements for a graduate degree from the University of North Dakota, I agree that the College of Nursing of this University shall make it freely available for inspection. I further agree that permission for extensive copying or electronic access for scholarly purposes may be granted by the professor who supervised my independent study work or, in her absence, by the chairperson of the department or the dean of the Graduate School. It is understood that any copying or publication or other use of this independent study or part thereof for financial gain shall not be allowed without my written permission. It is also understood that due recognition shall be given to me and to the University of North Dakota in any scholarly use which may be made of any material in my independent study.

Signature: _____

Date: _____

Abstract

This independent study is framed around a case report involving a young male requesting a cholesterol screening. Management of hyperlipidemia is imperative to reduce cardiovascular disease (CVD) risk. Yet, there are limited pharmacotherapeutic options available for the treatment and management of hyperlipidemia. Statin therapy is currently the first line option for increased cholesterol levels, though some people do not respond significantly enough or are unable to tolerate them due to adverse effects. These individuals would benefit from additional lipid-lowering therapy to ensure optimal cholesterol control and decreased cardiovascular disease risk. Proprotein convertase subtilisin kexin type 9 (PCSK9) enzymes are currently being targeted as an option to further control hyperlipidemia, as they have been found to play a role in cholesterol homeostasis. After reviewing the literature, the development of PCSK9 monoclonal antibodies is emerging as a promising new drug class with significant lipid-lowering capabilities when used in addition to statin therapy or as monotherapy. This paper discusses the importance of adequate cholesterol management in CVD risk reduction. The focus of this paper is geared toward the safety and efficacy of PCSK9 monoclonal antibodies and how this treatment approach may lead to more optimal cholesterol control and decreased CVD risk.

PCSK9 Monoclonal Antibodies:

Promising New Pharmacologic Therapy for the Treatment of Hyperlipidemia

A patient presents to your clinic requesting cholesterol screening with a known family history of premature cardiovascular death. This is significant because hyperlipidemia is an identified risk factor for cardiovascular disease. Individuals with known premature cardiovascular disease (CVD) or death among a first-degree relative are at an increased risk for premature cardiovascular disease themselves, as they may have a genetic component involved. Early recognition, screening, and treatment of hyperlipidemia are imperative in these individuals to ensure optimal lipid control and lifetime CVD risk reduction. Lifestyle modifications along with pharmacotherapy should be initiated at the time of diagnosis.

Statin therapy is currently the mainstay for treatment of hyperlipidemia, however there remain a significant number of people with elevated cholesterol levels that are unable to tolerate statins due to adverse effects, or individuals who are unable to attain optimal cholesterol reduction with statin therapy alone. This is very concerning, especially when patients have a high cardiovascular disease risk, as there are limited options available for these individuals to adequately treat and manage their hyperlipidemia. Joseph and Robinson (2015) found that “despite the optimal treatment with currently available therapies, 70-80% remain at high CVD risk and may benefit from additional LDL lowering” (p. 20).

A novel treatment approach is targeting proprotein convertase subtilisin kexin type 9 (PCSK9) enzymes to achieve lower blood cholesterol levels, specifically LDL, in order to help decrease the incidence of CVD. Research suggests that targeting PCSK9

enzymes is proving to be the most promising advancement in lipid-lowering therapy since the introduction of statins (Berthold, 2015). Though promising, PCSK9 monoclonal antibodies are typically used in addition to statin therapy or as a second line option.

Case Report

A twenty-four year old male patient was seen in the clinic requesting a cholesterol check due to a positive family history for hyperlipidemia. The patient reports that his father, a non-smoker, unexpectedly passed away from a heart attack at the age of forty-six while shoveling snow. The patient also notes that his brother, age thirty, has been diagnosed with high cholesterol, for which he is being treated for with pharmacotherapy. He denies any other significant family history such as diabetes, stroke, and cancer.

The patient is a non-smoker. He uses alcohol on occasion reporting one to two drinks during the month. His personal health history includes allergic rhinitis, and he has a past surgical history of a tonsillectomy and adenoidectomy at age four. He has no known drug allergies and currently only uses the medication Zyrtec as needed. He reports regular physical activity, working out four to five times weekly, which includes cardio and weight training. He notes that his diet includes a lot of fast food, and that he "eats out a lot".

His review of systems was negative, with special consideration involving the cardiovascular and respiratory systems. He denies chest pain, pressure, and palpitations at rest and with activity. He also denies shortness of breath, dyspnea with exertion, as well as orthopnea. Upon physical exam, his vital signs were as follows: blood pressure 110/54, heart rate 62 beats per minute, temperature 32.1 Celsius, height 6'1", and a weight of 200 pounds. His cardiovascular system demonstrated a regular rate and rhythm with S1 and

S2 present, and without murmur, rub, or click. His respiratory system revealed clear lung sounds throughout all lung fields upon auscultation, with a symmetrical chest rise and fall. A limited skin examination was negative for xanthomas and his skin was warm, dry, and intact.

Diagnostic tests that were ordered and performed included a fasting lipid panel to assess cholesterol levels as well as a fasting comprehensive metabolic panel (CMP) to check liver function, kidney function, blood glucose level and electrolytes. Results of the CMP all fell within the normal reference range. The lipid panel revealed a total cholesterol level of 310 mg/dL, a triglyceride level 140 mg/dL, a high-density lipoprotein (HDL) level of 60 mg/dL, and a low-density lipoprotein (LDL) level of 209 mg/dL

The diagnostic tests confirmed a diagnosis of hyperlipidemia, which could be familial, however further diagnostic testing, including genetic testing, would need to be completed. Recommended treatment includes moderate to intense statin therapy. Atorvastatin 20 mg by mouth nightly was prescribed to start. Side effects of the medication were discussed with the patient, specifically that of myalgias and the potential for increased liver enzymes. The patient was instructed to avoid grapefruit while on this medication as this can increase the risk of adverse drug effects. It was recommended that the patient continue to get at least thirty minutes of physical activity four to five times a week. Education was given concerning his diet and a referral to a dietician was addressed.

The patient should follow-up in the clinic in six weeks. At this time, he should have fasting blood work completed to recheck his liver function tests, and his LDL level.

A complete lipid panel should be rechecked in three-months. Depending on tolerance and lab values, therapy will be adjusted as needed.

Literature Review

A literature review was conducted using the PubMed database from the University of North Dakota's Harley French Library. Search terms utilized included "PCSK9," "hyperlipidemia," "hypercholesterolemia," "familial hyperlipidemia," and "treatment". Due to the novelty of the subject matter, limitations, such as dates, were not utilized. Ten articles, in total, were reviewed for this paper with all of them being published in 2015.

Hyperlipidemia and Cardiovascular Disease

Increased levels of LDL have a positive correlation with an increased risk of CVD. Decreasing LDL levels have proven to decrease CVD risk as evidenced by large randomized controlled trials (Whayne, 2015). With the introduction of statins, "numerous studies have shown that lowering LDL levels by statin therapy results in a reduction of cardiovascular mortality and morbidity" (Hartgers, Ray, & Hovingh, 2015, p. 19). Ezetimibe is the only non-statin drug that has been found to offer additional CVD event reduction when used as an add-on to statin therapy in high risk patients (Joseph & Robinson, 2015). Even with the introduction of statins, cardiovascular disease continues to be the leading cause of death, at 30% worldwide (Joseph & Robinson, 2015).

Familial hyperlipidemia (FH) is a condition in which genetic abnormalities result in decreased low-density lipoprotein receptor (LDL-R) function, thereby exposing the individual to extremely high LDL cholesterol levels. McKenney (2015) has found that patients with FH have "LDL levels about 4 times higher than in non-FH individuals" (p.

177). Decreased LDL-R function may be due to different genetic mutations that can cause LDL-R synthesis failure, inadequate LDL-R transport, ineffective LDL-R/LDL binding, and failure of LDL-R recycling depending on the specific mutation (Bouhairie & Goldberg, 2015). Individuals with FH are at a high risk for coronary artery disease (CAD) due to their increased LDL cholesterol. Bouhairie and Goldberg (2015) note that "CAD is the most common cause of premature death in these patients, but other cardiovascular diseases, including aortic and supravalvular aortic stenosis and aortic root disease, are also common" (p. 172).

Persons with FH require moderate to high intensity statin therapy; however, often times more than one medication is needed for optimal LDL reduction. When statin therapy is doubled, LDL cholesterol yields an additional reduction of only six to seven percent, and the potential for adverse drug effects is increased (Bouhairie & Goldberg, 2015). Hartgers et al. (2015) note "when using lipid-lowering therapy compared to non-FH subject, patients with FH were at a 10-fold risk for CAD" (p. 109). This emphasizes the importance of achieving optimal LDL cholesterol control in patients with FH as well as the increased need for more effective LDL lowering pharmacologic treatment options.

Statin therapy is the current recommended treatment for all individuals with hyperlipidemia, along with lifestyle modifications, which include a heart healthy diet rich in fruits and vegetables, physical activity, and smoking cessation. However, even with statin therapy and the implementation of lifestyle modifications, adequate lipid control is not always achieved. Depending on the statin dose, 20-70 percent of individuals do not achieve goal LDL levels (McKenney, 2015). In addition, some individuals are unable to take statins because of intolerance as a result of side effects such as myalgias and

impaired liver function. Not having adequate control of cholesterol places an individual at an increased risk for CVD.

Proprotein Convertase Subtilisin Kexin Type 9 Enzymes

Promising advances in the pharmacotherapeutic management of hyperlipidemia are currently being made. Novel treatment approaches are focusing their efforts on the PCSK9 enzymatic protein. The PCSK9 enzyme is primarily produced in the liver, and has proven to play a role in cholesterol homeostasis regulation.

PCSK9 enzymes bind with the LDL-R/LDL complex. The LDL-R/LDL complex is responsible for cholesterol regulation in that it is able to be internalized through endocytosis and then dissociated, at which point the LDL-R is recycled to repeat the process, and the LDL particle is degraded and released for stored cholesterol or other cellular activities (Joseph & Robinson, 2015). When the PCSK9 enzyme binds with the LDL-R/LDL complex this causes an irreversible bond of the three particles leading to complete lysosomal degradation of the LDL-R. This, in turn, yields a decrease in the amount of LDL-Rs available to bind with LDL resulting in increased plasma LDL cholesterol levels (Joseph & Robinson, 2015).

PCSK9 enzymes vary among individuals, and according to McKenney (2015) "significantly higher levels are reported in those with advancing age, female gender, postmenopausal status, higher body mass indices, high LDL levels, elevated triglyceride levels, higher insulin and glucose levels, diabetes, and higher C-reactive protein levels" (p. 171). One study found that "a composite endpoint of cardiovascular death and/or hospitalization was associated with increased PCSK9 levels" when the researchers

"measured serum PCSK9 levels in 504 clinically stable patients with angiographically proven coronary artery disease" (Whayne, 2015, p. 1).

Genetic mutations among the PCSK9 enzyme can lead to either hypercholesterolemia or hypocholesterolemia, depending on whether the mutation is characterized as loss of function (LOF) or gain of function (GOF). GOF PCSK9 mutations increase the uptake of LDL-R as a result of a greater binding affinity to the PCSK9 enzyme, thereby yielding an increase in total LDL cholesterol in the bloodstream. They also have been found to cause severe cases of heterozygous familial hyperlipidemia (HeFH) sometimes resulting in premature cardiovascular disease (Joseph & Robinson, 2015; McKenney, 2015). The opposite is true for LOF PCSK9 mutations, as they are "associated with low plasma LDL levels and a reduction in the incidence of adverse cardiovascular events" (Desai & Sabatine, 2015, p. 568).

Statin therapy has proven to be the hallmark of LDL lowering and cardiovascular risk reduction. Statins work by inhibiting cholesterol synthesis; this in turn induces the expression of sterol regulatory element binding protein-2 (SREBP2). SREBP2 induces PCSK9 gene expression leading to a positive correlation between statin therapy and increased PCSK9 enzymes, which hinders the efficacy of statin treatment (Bergeron, Phan, Ding, Fong, & Krauss, 2015). Desai and Sabatine (2015) note, "depending on the intensity, statin therapy will increase circulating PCSK9 levels by close to 50%" (p. 568). Increased lipid-lowering capability may occur by being able to inhibit the action of PCSK9 enzymes in addition to treatment with statin therapy.

PCSK9 monoclonal antibodies

Understanding the mechanism of action of PCSK9 enzymes has driven the development of novel drug therapies to aide in the reduction of LDL cholesterol utilizing PCSK9 inhibition. To date, PCSK9 monoclonal antibodies have proven to be the most advanced approach to this concept with phase III clinical trials currently being and have been completed (Bergeron et al., 2015). Results of these studies have found that PCSK9 antibodies have an efficacy "equal to or greater than statin therapy for decreasing LDL" marking its importance due to resistance or adverse effects of statins in some patients (Whayne, 2015, p. 4).

The monoclonal antibodies for PCSK9 inhibition work by binding to the PCSK9 enzymes and suppressing their activity. This action prevents them from being able to bind to the LDL-R. The LDL-Rs are then uninhibited and their function is restored, therefore, leading to increased hepatic uptake of circulating LDL, which then results in a decreased total LDL within the bloodstream (McKenney, 2015).

As of 2015, the United States Food and Drug Administration (FDA) has approved two PCSK9 monoclonal antibodies for use: alirocumab and evolocumab. The PCSK9 monoclonal antibodies have proven to be generally well tolerated because they are fully humanized antibodies, which decrease the risk potential for immune reactions (Berthold, 2015; Stein and Raal, 2015). They have been found to be highly target specific and they have a long serum half-life. McKenney (2015) notes that they "have limited potential for drug-drug interactions due to their target specificity" and "they neither interact with cytochrome P450 or other transport proteins in the body nor affect the QT interval changes" (p. 21).

Extensive research has been done regarding the safety and efficacy profiles of these drugs, with both of these drugs having been studied in phase I, II, and III clinical trials. Both drugs have similar safety and tolerability profiles with injection site reactions being the most common adverse affect occurring in two to five percent of the patient population (McKenney, 2015). Also, there is no evidence that the use of these drugs increases the prevalence or intensity of muscle related adverse effects as seen with statin therapy use (Berthold, 2015; McKenney, 2015). Another important finding is that there is no sign that PCSK9 inhibition has a negative affect on hepatic or renal function (Berthold, 2015; Verbeek, Stoekenbroek, & Hovingh, 2015). This eliminates the need for routine lab monitoring, and does not pose contraindications for use in patients with liver disease or decreased kidney function. Currently PCSK9 monoclonal antibodies are only available via intravenous or subcutaneous administration.

Many different populations have been studied using the PCSK9 monoclonal antibodies of alirocumab and evolocumab during the phase III clinical trials. These populations include, but are not limited to, patients unable to tolerate statin therapy, hypercholesterolemic patients on background statin therapy, hypercholesterolemic patients that are not on any lipid-lowering medications, and patients with heterozygous and homozygous familial hypercholesterolemia (Bergeron et al., 2015).

Alirocumab. Results of phase I and II clinical trials for alirocumab were significant in that they demonstrated "dose-dependent reductions in LDL of 50% as a monotherapy and up to 65% as an add-on therapy to statins" (Joseph & Robinson, 2015, p. 23). This prompted further research and the Odyssey phase III clinical trial program was launched. This program is derived of fourteen studies that look at the effect that

alirocumab has on LDL cholesterol among the different populations as stated above. Each of the trials determined that the use of alirocumab resulted in an increased reduction of LDL cholesterol levels when used as an add-on to statin therapy, and is superior to other lipid-lowering agents, such as ezetimibe, in patients who are intolerant to statins or who are on a maximally tolerated statin dose and need increased LDL lowering capacity to reach goal (Joseph & Robinson, 2015; McKenney, 2015).

Alirocumab was the first PCSK9 monoclonal antibody to be approved in the United States by the FDA. The FDA has approved alirocumab "for use in addition to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia or patients with clinical atherosclerotic cardiovascular disease such as heart attacks or strokes, who require additional lowering of LDL cholesterol" (Bergeron et al., 2015, p. 1660-1661). The recommended dose is a 75 mg subcutaneous injection every two weeks.

Evolocumab. Evolocumab has proven to be a highly efficacious option for LDL lowering use, as well. Joseph and Robinson (2015) noted the following:

> In phase I and II clinical trials, evolocumab emerged as an efficacious and safe option for LDL reduction as monotherapy or as add on therapy to statin, in statin intolerant patients, in high CVD risk patients as well as the HeFH population. (p. 25).

Reductions in LDL cholesterol were dose dependent with as much as a 51% reduction seen when evolocumab was used as monotherapy, and up to a 66% reduction of total LDL was seen when used as an add-on therapy to statins (Joseph & Robinson, 2015). A series of phase III clinical trials known as Proficio were conducted to provide further

research and evidence regarding the use of evolocumab among the different patient populations. This program consisted of twenty-two different phase III clinical trials. As with alirocumab, the studies found that the LDL lowering capacity of evolocumab in addition to statin therapy was substantial, and that it was superior in LDL cholesterol reduction to other lipid lowering agents in patients that are unable to take statins or who are already on the maximal statin dose (Joseph & Robinson, 2015).

The FDA approved evolocumab in August of 2015. It was approved for use "in addition to diet and maximally-tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia, homozygous familial hypercholesterolemia, or clinical atherosclerotic cardiovascular disease, such as heart attacks or strokes, who require additional lowering of LDL cholesterol" (Bergeron et al., 2015, p. 1661). Evolocumab is recommended as a subcutaneous injection of 140 mg every 2 weeks or 420 mg once monthly.

PCSK9 Monoclonal Antibodies and Cardiovascular Disease

Currently there are two long-term phase III clinical trials that test the efficacy and safety of aliromucab and evolomucab and their ability to reduce vascular adverse events specifically. Desai and Sabatine (2015) note:

> The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (Fourier) study is assessing whether treatment with evolocumab compared to placebo reduces recurrent cardiovascular events in approximately 27,500 patients with established cardiovascular disease. The Odyssey Outcomes trial is examining the impact of alirocumab on major adverse cardiovascular events among patients who have recently experienced an acute

coronary syndrome, and it is expected to enroll 18,000 patients. (p. 571).

These trials will help to provide more information regarding the risk reduction potential that PCSK9 monoclonal antibodies may have on CVD.

Future Considerations for PCSK9 Monoclonal Antibodies

One concern that researchers are having is whether or not LDL cholesterol can become too low and potentially have detrimental side effects. Some studies have seen LDL levels decrease to <25 mg/dL in patients that are on maximum statin therapy with PCSK9 monoclonal antibody add-on therapy (Joseph & Robinson, 2015). However, they point out that "healthy individuals with homozygous PCSK9 loss-of-function mutations who have had lifetime LDL levels as low as 14-16 mg/dL have remained healthy" (Joseph & Robinson, 2015, p. 22). This suggests that very low LDL levels do not pose significant risk among the individual, though more research in the future may be warranted.

Learning Points

Research concerning PCSK9 monoclonal antibodies and their effect on LDL cholesterol and CVD risk reduction is ongoing. Completed studies have demonstrated promising results with two PCSK9 monoclonal antibodies having gained approval for use in the United States by the FDA in 2015. Advancements for the treatment of hyperlipidemia are not only imperative but also exciting. The importance of this novel treatment option is implicated in the following ways:

- even with the use of statin therapy, CVD continues to be the worldwide leading cause of death;

- for patients intolerant to statins or those unable to achieve optimal LDL control on a maximally tolerated statin dose, pharmacotherapeutic options for additional hyperlipidemia management are limited;
- optimal LDL control results in a decreased risk of CVD or CVD related death in at risk individuals;
- the action of PCSK9 monoclonal antibodies result in an increased amount of LDL-Rs available for the uptake of LDL cholesterol, therefore decreasing the amount of LDL cholesterol present in the bloodstream;
- PCSK9 monoclonal antibodies have proven to be a safe and effective treatment option for LDL cholesterol lowering when used in addition to statin therapy or as monotherapy.

References

Bergeron, N., Phan, B., Ding, Y., Fong, A., & Krauss, R., (2015). Proprotein convertase subtilisin/kexin type 9 inhibition: A new therapeutic mechanism for reducing cardiovascular risk. *Circulation, 132,* 1648-1666. doi:10.1161/circulationaha.115.016080

Berthold, I., (2015). PCSK9 antibodies: A new class of lipid-lowering drugs. *Atherosclerosis Supplements, 18*(2015), 21-27. http://dx.doi.org/10.1016/j.atherosclerosissup.2015.02.003

Bouhairie, V. E., & Goldber, A. C. (2015). Familial hypercholesterolemia. *Cardiology Clinic, 33*(2015), 169-179. http://dx.doi.org/10.1016/j.ccl.2015.01.001

Desai, N. R., & Savatine, M. S., (2015). PCSK9 inhibition in patients with hypercholesterolemia. *Trends in Cardiovascular medicine, 25*(2015), 567-574. http://dx.doe.org/10.1016/j.tcm.2015.01.009

Hartgers, M. L., Ray, K. K., & Hovingh, G. K., (2015). New approaches in detection and treatment of familial hypercholesterolemia. *Current Cardiology Reports, 17*(2015), 109. doi:10.1007/s11886-015-0665-x

Joseph, L., & Robinson, J. G., (2015). Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition and the future of lipid lowering therapy. *Progress in Cardiovascular Diseases, 58*(2015), 19-31. http://dx.doi.org/10.1016/j.pcad.2015.04.004

Mckenney, J. M., (2015). Understanding PCSK9 and anti-PCSK9 therapies. *Journal of Clinical Lipidology, 9*(2015), 170-186. http://dx.doi.org/10.1016/j.jacl.2015.01.001

Stein, E. A., & Raal, F. J., (2015). Lipid-lowering drug therapy for CVD prevention:

Looking into the future. *Current Cardiology Reports, 17*(2015), 104. doi:10.1007/s11886-015-0659-8

Verbeek, R., Stoekenbroek, R., & Hovingh, G., (2015). PCSK9 inhibitors: Novel therapeutic agents for the treatment of hypercholesterolemia. *European Journal of Pharmacology, 763*(2015), 38-47. http://dx.doi.org/10.1016/j.ejphar.2015.03.099

Whayne, T. F., (2015). Defining the role of PCSK9 inhibitors in the treatment of hyperlipidemia. *American Journal of Cardiovascular Drugs, 2015,* 1-10. doi:10.1007/s40256-015-0150-3