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Proprotein Convertase Subtilsin-Kexin Type 9 Inhibitor Use for the Treatment of Hyperlipidemia

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University of North Dakota

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Title  Proprotein convertase subtilisin-kexin type 9 inhibitor use in the management of hyperlipidemia

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Abstract

Heart disease remains the number one cause of death for Americans. Stringent cholesterol management has proven to be the single most modifiable risk factor in the prevention of cardiovascular disease. Statins remain the current treatment of choice in the management of hyperlipidemia, however not all patients are able to achieve optimal cholesterol control with the use of statin therapy alone. Recent development of a novel class of drugs, proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors, has proven beneficial in the management of high cholesterol for patients resistant or intolerant to statin therapy. Herein, we will report a case of a 45-year-old female with a diagnosis of hyperlipidemia currently not managed with statin therapy. We will further explore the novel class of PCSK9 inhibitors in the management of hyperlipidemia.

Using the University of North Dakota’s Harley French medical library, a search was completed to further explore this novel class of medication. Search methods utilized included CINAHL, PubMed, and DynaMed Plus database searches. Initially 619 articles were identified matching the search criteria. This search was further narrowed down by limiting the search parameters to full text articles, those published in English, articles published in the last 5 years, and peer reviewed articles. This narrowed the search down to 171 articles. Combining key words to narrow the search further reduced the articles to 45 for review. This was further narrowed down to 16 articles applicable to the topic at hand for inclusion in this case discussion. Key words utilized during this search included proprotein convertase subtilisin/kexin type 9 inhibitors, low-density lipoproteins, hyperlipidemia, and PCSK9 inhibitors.

Background
Heart disease remains the leading cause of death in America, resulting in approximately 610,000 deaths per year. (Center for Disease Control and Prevention, 2017). Management of low-density lipoprotein cholesterol has been proven to be a major modifiable risk factor in the development of cardiovascular disease. Primary care providers play a pivotal role in the management of hyperlipidemia, which is often confounded by other comorbid patient conditions making achieving goals in cholesterol management particularly challenging (Shimada & Cannon, 2015).

Statin therapy for the management of hyperlipidemia has been the cornerstone in treatment since their development, proving effectiveness in reducing cardiovascular risks for patients with high cholesterol (Chaudhary, Garg, Shah, & Summer, 2017). Although statins have been proven effective in lowering LDL cholesterol levels for many patients, there remain many unmanaged with statin therapy alone, requiring the implementation of additional therapies in order to achieve target LDL levels. Adverse effects related to statin therapy may further limit their use in the management of hyperlipidemia. The recent development of a new class of drugs, the proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors, have shown promising results in lowering LDL levels, leading to more options in the management of patients with hyperlipidemia (Hess, Wang, & Hiatt, 2018).

**Case Report**

A.G. a 45-year-old Caucasian female, with a history significant for type 2 diabetes, hyperlipidemia, and hypertension, presented to the clinic for a diabetes recheck. She was diagnosed with diabetes after a routine screening during her last annual physical approximately three months ago. She recently met with the diabetic educator to help manage her new diagnosis.
The diabetic educator recommend she follow up with her primary care provider for further evaluation and management.

Her current medication regimen includes Metformin 500mg twice a day; Aspirin 81mg daily; Lisinopril 20mg daily, Atorvastatin 20mg daily; and a daily multivitamin. She reports occasional acetaminophen use as needed for headaches. She has an allergy to penicillin. She denies use of nicotine, alcohol, or recreational drugs. She reports that she is up to date on all of her immunizations. Her chief complaint now is increasing fatigue and a 20lb weight gain over the last 2 months. She reports that she feels tired every day of the week despite adequate rest at night. She reports significant stress related to her current job as a clerk at the court house. She has a family history significant for hyperlipidemia and cardiovascular disease. She reports eating three meals a day with occasional snacks throughout the day. She frequently goes out to eat due to the convenience of not having to cook. She has not been able to exercise routinely due to lack of time and fatigue. Her blood sugars at home have been varying between the 150s to low 200s.

On exam, she is well-appearing and is in no acute distress. No significant abnormalities were noted on physical exam except mild decreased sensation to both of her lower extremities. Her vital signs are as follows; temperature 98.6, blood pressure 148/98, heart rate 80, respiratory rate 20. Labs were obtained during her visit to further investigate her fatigue and weight gain. For the sake of brevity, only relevant labs are included in this document and are as follows:

- Hemoglobin A1C 8.5% (Normal <6%)
- Cholesterol panel
  - HDL cholesterol 43 mg/dl (normal for females >50 mg/dl)
  - LDL cholesterol 133mg/dl (normal range: <100 mg/dl)
  - Triglycerides: 180 mg/dl (normal range: <150 mg/dl)
- Thyroid stimulating hormone 6.4 (normal range 0.4-4)
- Glucose: 178 mg/dl (normal 70-99 mg/dl)

Assessment of this patient revealed poorly controlled diabetes, subclinical hypothyroidism due the mild elevation in her TSH level, dyslipidemia, and hypertension. In order to improve the patient’s overall health and quality of life, an in depth conversation between the patient and the clinician lead to the initiation of a daily low dose of levothyroxine to see if that would resolve some of her complaints. Education on the importance of a balanced diet and exercise, and a referral to a dietician was made in an attempt to improve the patient’s hypertension, diabetes, and high cholesterol.

Due to the patient’s increased risk of cardiovascular events from her underlying diabetes, management of her hyperlipidemia is of increased importance. Her current hyperlipidemia treatment has not resulted in therapeutic cholesterol ranges leaving her at an even higher risk for cardiovascular events.

**Literature Review**

Heterozygous familial hypercholesterolemia is an autosomal co-dominant genetic disorder resulting in high low-density lipoprotein cholesterol levels from birth. This disorder increases an individual’s risk of premature cardiovascular events as it exposes the arteries to significantly higher levels of cholesterol leading to endothelial damage and plaque build-up, resulting in arterial narrowing and increased risk of thrombotic events (Cataplana, Pirillo, & Norata, 2017).

Familial hypercholesterolemia is the most frequently diagnosed lipid disorder in children and adolescents occurring approximately 1 in 500 individuals in the United States. Patients with this familial hypercholesterolemia rarely show signs or symptoms. Xanthelasma or lipid deposits may be noted on the skin during patient assessment. Other subtle clues may be noted on exam
including corneal arcus, which is seen as a grayish white opaque ring on the outer cornea of the eye, and swelling of the Achilles tendon (DynaMed, 2018).

Early identification of patients with a familial hypercholesterolemia is essential to the prevention of cardiovascular events. Screening should start by obtaining an accurate family history to assess for familial incidence of hyperlipidemia. Patient history could be another clue to this disorder. Patient with premature cardiovascular disease have a high correlation with familial hypercholesterolemia. Patients identified as high risk should have further diagnostics to determine incidence of hyperlipidemia. Elevation of a patients LDL cholesterol level on two consecutive fasting screenings confirms a diagnosis of hyperlipidemia. Patients with a significant family history of hyperlipidemia may further benefit from genetic screening to confirm a diagnosis of familial hypercholesterolemia. However, genetic testing is not necessary to confirm a diagnosis of for management of the disorder (DynaMed, 2018).

Initial management of hyperlipidemia revolves around lifestyle modifications. Recommended modifications include reducing the overall consumption of saturated fats and refined carbohydrates in the diet, increased physical activity and smoking cessation. Statin therapy is currently the drug of choice in the management of high cholesterol with a target LDL level of less than 70 after treatment initiation. Statin therapy is titrated up to the maximum dose tolerated and if needed the addition of ezetimibe is trialed in attempt to achieve LDL goals. Patients that do not respond significantly to initial treatment options should be considered for PCSK9 inhibitor use (Svátková & Kopecký, 2017).

Patients with heterozygous familial hypercholesterolemia are often resistant to treatment with statin therapy, making achieving target cholesterol levels difficult. Adjunct therapy with the use of PCSK9 inhibitors have proven beneficial in the management of patients with high cholesterol
PROPROTEIN CONVERTASE SUBTILSIN-KEXIN TYPE 9 INHIBITORS

(Catapano et al., 2017). PCSK9 is an enzyme important in the metabolism of LDL cholesterol. It is primarily excreted by the liver, binding to the low density lipoprotein receptors on the liver cells. This triggers the breakdown of the low density lipoprotein receptor, resulting in an elevated plasma LDL levels (Kastelein, Stroes, Stiekema, & Rosenson, 2017). The importance of the PCSK9 gene in cholesterol management was first identified in 2003 when patients with familial hypercholesterolemia were noted to have an associated overexpression of PCSK9, leading to higher overall cholesterol and LDL levels. Patients with loss of PCSK9 function as a result of gene mutations, were further shown to have lower cholesterol levels and lower risk of cardiovascular disease overall (Hess et al., 2018).

In 2015, the Food and Drug Administration approved two PCSK9 inhibitors, Alirocumab and evolocumab, for the treatment of primary hypercholesterolemia in conjunction with diet and statin therapy (Noel & Beavers, 2016). These medications promote the breakdown of the PCSK9 enzyme, resulting decreased free PCSK9 available to bind with the low density lipoprotein receptor increasing the livers ability to remove more LDL from the blood (Kastelein et al., 2017).

Randomized trials have further proven the benefit in initiating treatment with PCSK9 inhibitors to decrease patient mortality from cardiovascular events overall. Studies have shown a significant reduction in LDL cholesterol levels of up to 70% (Kastelein et al., 2017). Besides the lipid lowering ability of PCSK9 inhibitors, other cardioprotective mechanisms have been identified. It has been postulated that these medications decrease inflammation and oxidative stress within atherosclerotic plaques. They further interrupt the prothrombotic pathways in the body, which may prove beneficial to patients with underlying acute coronary syndrome (Kastelein et al., 2017).
PCSK9 inhibitors have proven effective in the management of other aspects of a patient’s lipid panel besides the management of LDL cholesterol levels. Kastelein et al. (2017) report varying decreases, ranging from 12 to 31 percent, in triglyceride levels noted in patients using PCSK9 inhibitors for cholesterol management. Mild increases in high density cholesterol levels ranging between 5 to 9 percent have been further noted with these medications. The significant benefit in the overall improvement in patients’ cholesterol levels has shown to decrease patients’ overall atheroma volume, eluding to a significant reduction in cardiovascular event risk of up to 50% (Kastelein, Stroes, Stiekema, & Rosenson, 2017).

Even though PCSK9 inhibitors have shown great efficacy in the lowering of LDL levels and preventing cardiovascular events in patients with hyperlipidemia, these agents remain second line therapy in cholesterol management after statin use, primarily due to cost. Recommendations for the use of PCSK9 inhibitors should be made on an individual basis, weighing the risks and benefits of therapy with these medications. Screening for high risk patients, including those with a family history of hyperlipidemia and those at high risk for cardiovascular events unable achieve ideal LDL levels with other treatment options, helps identify individuals most appropriate for use of PCSK9 therapy.

Administration of PCSK9 inhibitors are given as a subcutaneous injection in a variety of dosing regimens ranging from every two weeks to monthly dosing improving patient compliance overall (Kastelein et al., 2017). Recommended dosing for Evolocumab is 140mg subcutaneously every two weeks or 420mg monthly for the management of hyperlipidemia (Truven Health Analytics, 2016). Alirocumab therapy is initiated at 75mg subcutaneously every two weeks. Treatment can be titrated up as needed in order to achieve LDL cholesterol goals with a maximum dose of 150mg every two weeks (Truven Health, 2015). The primary role of both of
these medications is in the treatment of homozygous familial hypercholesterolemia not managed by maximally tolerated statin therapy. Adverse effects from statin therapy including severe myalgias, increased incidence of diabetes mellitus, and liver failure may preclude PCSK9 inhibitor use (Hess et al, 2018). Safety and efficacy of PCSK9 inhibitors is another important benefit to their use. LDL cholesterol levels should be monitored every 4-8 weeks upon therapy initiation to ensure goal cholesterol levels are achieved and to titrate medication dosages. No further lab monitoring is warranted with continued use. To date, no drug-drug interactions or drug-food interactions have been identified with use of these medications, increasing their safety in the management of patients with multiple comorbidities (Kosmas et al., 2017).

Both Alirocumab and Evolocumab have been approved for adult use in the management of hyperlipidemia. Evolocumab has been approved for use in pediatric patients over the age of 13 years old. Safety for use in expectant mothers or those breastfeeding has not been identified. (Truven Health, 2015). No major adverse effects from the use of PCSK9 inhibitors have been identified to date. Allergic reactions have been identified as one of the major reactions in sensitive patients. Non-specific adverse events with the use of PCSK9 inhibitors may include injection site reactions, arthralgias, headaches, limb pain, nasopharyngitis, upper respiratory infections, and fatigue (Kosmas et al., 2017). It has been hypothesized that prolonged management of hyperlipidemia with the PCSK9 inhibitor class may result in extremely low LDL levels resulting in negative neurocognitive function as cholesterol is essential for normal synapse formation and function in the brain. It should further be noted that the blood-brain barrier is thought to protect patients from neurocognitive changes as PCSK9 are unable to cross the blood-brain barrier. More research is needed to determine the long term implications of PCSK9 use (Pandey, Bajaj, Garg, Pandey, & Verma, 2017).
Patient education is extremely important when prescribing PCSK9 inhibitors. Patients with latex allergies should be warned that some of the injectors for medication administration may contain natural rubber products. To avoid possible life threatening reactions, patients should discuss latex free administration options with their pharmacist when starting PCSK9 therapy (Truven Health, 2015). Patients should be educated on the possible side effects of these medications although often rare and mild. Side effects including nasopharyngitis, upper respiratory infections, influenza, back pain, and injection site reactions should be discussed with patients prior to use. Proper administration techniques and injection site placement is another important highlight for providers to review with patients. If a patient inadvertently misses a dose of medication the medication should be administered as soon as possible if the next dose due is greater than 7 days out. For those that remember a missed dose with less than 7 days until the next dose that dose should be skipped and the dosing regimen started with the next dosing scheduled (Truven Health, 2016).

One of the major challenges with the implementation of PCSK9 therapy is cost. Retail cost of these medications average around $14,000 per year (Saeed et al., 2017). Many insurance companies have further restricted use of these medications, limiting use to patients at high risk for cardiovascular disease and who have met the stringent requirements for use, including not achieving LDL levels with statins alone or those intolerant of statin use. Preapproval is recommended prior to use of these medications to avoid costs to patients (Saeed et al., 2017).

**Conclusion**

Early identification and management of patients with familial heterozygous hypercholesterolemia is paramount in the prevention of cardiovascular disease and
cardiovascular events. Patients resistant to statin therapy may benefit from PCSK9 inhibitor use in order to achieve adequate cholesterol control.

A.G. had been previously diagnosis with hyperlipidemia. Her concurrent medical conditions, including diabetes and hypertension, put her at an even greater risk for the development of cardiovascular disease and cardiovascular events, including stroke and heart attack. With her significant family history of hyperlipidemia it can be assumed, that she has underlying heterozygous familial hypercholesterolemia, making treatment challenging.

Several attempts were made to try and achieve goal a LDL cholesterol level. Initially life style modifications were tried with very little success. She was started on statin therapy after failing treatment with lifestyle management alone. Statin therapy helped to lower her LDL level after initiation, however, her level remained significantly above management goals. Statin therapy was titrated in attempt to achieve therapeutic cholesterol levels, only to result in significant myalgias for A.G. The addition of ezetimibe was trialed with the lower dose of statin therapy with little success.

After a though discussion with A.G., weighting the risks and benefits of cholesterol management with PCSK9 inhibitor use, it was decided to start the preapproval process with her insurance company in an attempt to initiate PCSK9 inhibitor therapy. After enduring several months of the preapproval process, she was approved for use of PCSK9 therapy. She was initiated on evolocumab 140mg every two weeks while continuing the highest tolerable dose of her statin therapy. After eight weeks of therapy she was able to reach target LDL cholesterol levels with the addition of PCSK9 inhibitor therapy, further reducing her risk of cardiovascular disease.

**Learning Points**
Heterozygous familial heterozygous hypercholesterolemia is a relatively common condition presenting challenges in the management of hyperlipidemia.

Patients unable to tolerate side effects from statin therapy or those that are unable to achieve LDL cholesterol goals should be considered for PCSK9 inhibitor use.

Due to their significant cost and stringent preapproval process, PCSK9 inhibitors should be reserved for patients who have failed to achieve cholesterol management with other therapies.
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