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Objectives

After completion of this program, the reader should be able to:

1. Describe the mechanism of action of PCSK9 inhibitors.
2. Identify FDA approved indications for alirocumab (Praluent®) and evolocumab (Repatha®).
3. Review clinical trials involving PCSK9 inhibitors and identify potential adverse effects and significant clinical outcomes.
4. Explain the appropriate storage, use and administration of PCSK9 inhibitors for patient discussion.

Abstract

The recent U.S. Food and Drug Administration (FDA) approval of two new drugs, alirocumab (Praluent®) and evolocumab (Repatha®) is a breakthrough in the treatment of familial hypercholesterolemia. These drugs are a part of a new class called the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors that act by increasing the number of low density lipoprotein receptors (LDL-R) recycled to hepatocyte membranes. The increased density of LDL-R facilitates greater clearance of low density lipoproteins from the blood. Numerous clinical trials have demonstrated the efficacy of these agents, particularly for patients in whom standard cholesterol-lowering therapy is insufficient. However, data on long-term health outcomes in patients on PCSK9 inhibitors will not be known for several years. Opportunities for pharmacists include counseling on how to store and administer the medication, helping patients receive access to therapy and advocating for healthy lifestyle changes. Pharmacists should also be aware of insurance coverage and emerging indications for each agent in order to provide the best care for patients.

Key Terms

Antibodies; Cholesterol; Hypercholesterolemia; Human; Monoclonal; PCSK9 Protein

Introduction

Today's healthcare environment is dominated with concerns relating to obesity and high cholesterol. The current mainstays of therapy for these conditions are decades old and do not provide many patients with sufficient benefit to maximally reduce associated morbidity and mortality. Novel agents that affect lipid levels are necessary to improve outcomes, not only in patients with hyperlipidemia associated with a sedentary lifestyle and poor dietary habits, but also in patients with genetic conditions such as heterozygous and homozygous familial hypercholesterolemia (HeFH, HoFH). Many of these patients fail to reach or maintain sufficient reductions in cholesterol levels on standard lipid-lowering therapies, leading to increased morbidity and mortality. A new class of lipid-lowering agents, the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, are able to induce significant reductions in low-density lipoprotein cholesterol (LDL-C) relative to statins and ezetimibe.[1,2] This article seeks to describe the mechanism and efficacy of these new agents as well as their future role in the management of patients with hypercholesterolemia.

Pharmacology

Both low density lipoprotein receptors (LDL-R) and PCSK9 are synthesized in hepatocytes under sterol regulatory element-binding protein 2.[3,4] The N-terminus of PCSK9, responsible for proper folding of the enzyme, is cleaved in the endoplasmic reticulum, but remains attached to PCSK9 in the catalytic site to inhibit other substrates from binding to it. The PCSK9 is then packaged and secreted by the golgi apparatus into the plasma, where it can bind LDL-R via the epidermal growth factor domain A (EGF-A). This initiates the endocytosis and lysosomal degradation of the PCSK9-LDL-R complex by an unknown mechanism (Figure 1a). When PCSK9 is overexpressed, this action results in fewer LDL-R recycled to the hepatocyte membrane, and a corresponding increase in LDL-C levels.

Alirocumab and evolocumab are monoclonal antibodies that bind to PCSK9 to inhibit its binding to the LDL-R (Figure 1b). They also allow the receptor to be recycled back to the surface of the hepatocyte membrane. Both drugs have been approved for the treatment of familial hypercholesterolemia and clinical atherosclerotic cardiovascular disease (ASCVD), in addition to a low fat diet and maximally tolerated statin therapy.[5,6] Both drugs have shown superior efficacy and safety profiles compared to the standard treatment, which includes a high dose statin (atorvastatin 80 mg or rosuvastatin 40 mg), ezetimibe and/or niacin with a low fat diet.[7]

In patients with familial hypercholesterolemia, LDL-C levels are commonly uncontrolled with high dose statins and adjunct therapy with a second cholesterol lowering agent, therefore, morbidity and mortality remain high. Statins work to inhibit cholesterol synthesis, but only modestly reduce LDL-C levels in some patients. Ezetimibe inhibits cholesterol absorption in the small intestine via inhibition of the Nie-

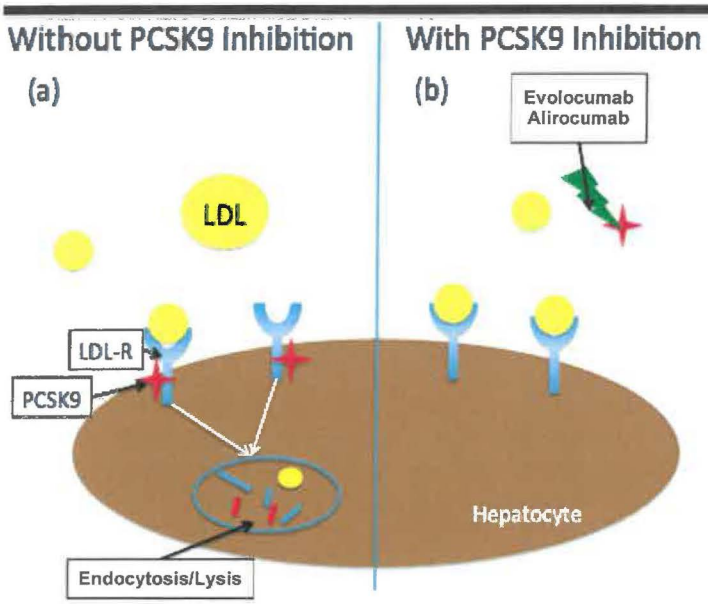

Figure 1.
(a) Proprotein convertase subtilisin/kexin type 9 (PCSK9) normally binds to the low density lipoprotein receptor (LDL-R) to induce its endocytosis and lysosomal degradation when LDL binds to the LDL-R.
(b) Evolocumab or alirocumab binds to PCSK9 extracellularly to inhibit PCSK9 from binding to the LDL-R.

mann-Pick C1-Like 1 transporter to prevent cholesterol from reaching the hepatic circulation.[8] Statins and ezetimibe are usually prescribed as dual therapy with the option of substituting niacin for ezetimibe. However, the mechanism of niacin is not well understood, and it is not as commonly prescribed. Newer treatments include lomitapide, a microsomal triglyceride transfer protein inhibitor and mipomersen, an inhibitor of mRNA coding of apolipoprotein B-100.[9] At over $34,000 and $6,000 per dose, respectively, the costs of lomitapide and mipomersen are far greater than either evolocumab and alirocumab, which each cost about $600 per dose.[10-13] These newer agents are also not as well studied as the PCSK9 inhibitors.

Trial Data: Alirocumab
Numerous studies have been conducted that illustrate the efficacy of PCSK9 inhibitors. The Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM) trial examined the efficacy and safety of alirocumab in reducing lipids and cardiovascular events over a period of 78 weeks.[1] This trial included 2,341 patients who had LDL-C levels of greater than 70 mg/dl, at risk for cardiovascular events and receiving treatment with statins at the highest tolerated dose with or without other lipid-lowering therapy. Patients had coronary heart disease, a disease equivalent in cardiovascular risk, or HeFH.

The mean calculated LDL-C level was 122 mg/dL at baseline, with a goal LDL-C level of less than 70 mg/dL.[1] Subjects were randomly assigned to receive 150 mg subcutaneous injection of alirocumab or placebo every two weeks for 78 weeks with concomitant statin and other lipid-lowering therapy, if applicable, throughout the study. Follow ups were conducted at weeks 12, 24, 52 and 78 to assess safety and adherence and to perform lab tests to determine the efficacy of the drug. The primary endpoint was the change in calculated LDL-C levels from baseline to week 24. Safety endpoints were adverse events, including symptoms and laboratory abnormalities occurring up to week 10.

At week 24, the mean percentage change in calculated LDL-C levels were -61.0 percent for the alirocumab group versus 0.8 percent in the placebo group ($p < 0.001$).[1] The mean absolute LDL-C level at week 24 was 48.3±0.9 mg/dL and 119±1.2 mg/dL in the alirocumab and placebo groups, respectively. Investigators also found that 79.3 percent of patients in the alirocumab group met the goal LDL-C level of less than 70 mg/dL versus only 8 percent of patients in the placebo group ($p < 0.001$). Reduction of the LDL-C levels in the alirocumab group persisted through the end of the trial.

The percentage of patients who experienced any adverse reactions was not found to be statistically significant.[1] Most of the reported reactions were related to pain at the injection site, or a general allergic reaction. Alirocumab had higher rates of injection-site reactions, myalgia, neurocognitive events and ophthalmologic events than placebo. In the alirocumab group, 18.7 percent of patients reported a serious adverse event versus 19.5 percent in the placebo group. However, most of the adverse events leading to subject dropout were not considered serious.

In conclusion, more evidence needs to be collected to determine alirocumab's impact on long-term risk of cardiovascular events. The ongoing trial ODYSSEY OUTCOMES is focused on providing these long-term cardiovascular outcome data and is expected to be completed near December of 2017.[14,15]

Trial Data: Evolocumab
Goal Achievement after Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects (GAUSS-2) assessed the efficacy and safety of evolocumab.[2] The study included 307 patients currently receiving no or low-dose statins who had previous intolerance to two or more statins. Subjects were divided into four groups with different medication regimens:

Group 1: Evolocumab 140 mg subcutaneous injection every two weeks with oral placebo.
Group 2: Evolocumab 420 mg subcutaneous injection every month with oral placebo.
Group 3: Ezetimibe once daily with subcutaneous injection of placebo every two weeks.
Group 4: Ezetimibe once daily with subcutaneous injection of placebo every month.

Primary endpoints were the change in LDL-C levels from baseline to the mean of weeks 10 and 12. The mean baseline LDL-C level was 193 mg/dL. Primary safety endpoints included serious adverse events and elevations in hepatic enzymes and creatinine kinase.

At weeks 10 and 12, the LDL-C reductions from baseline were 56.1 percent in group 1, 55.3 percent in group 2, 36.9 percent in group 3, and 38.7 percent in group 4.[2] More than 75 percent of the evolocumab-treated patients versus less than 10 percent of the ezetimibe-treated patients were able to achieve LDL-C levels of less than 100 mg/dL.

Additionally, this study did not find any significant elevations in liver enzyme tests or creatinine kinase levels.[2] Adverse events leading to treatment discontinuation occurred in 8 percent of evolocumab treated patients and 13 percent of ezetimibe treated patients. Only 6 percent of reported adverse events were considered serious. Myalgia was reported in 8 percent of evolocumab treated patients and 18 percent of ezetimibe treated patients. Patients taking low dose statins were more likely to report myalgia.

RedUction of LDL-C with PCSK9 InhibiTion in HEteRozygous Familial HyperchOlesteRolemia Disorder (RUTHERFORD-2) evaluated the effects of PCSK9 inhibition with evolocumab in subjects with HeFH.[16] All 331 patients had a clinical diagnosis of HeFH, had been on a statin with or without other lipid-lowering therapy for at least 4 weeks prior to the study and had a fasting LDL-C concentration of 2.6 mmol/L (100 mg/dl) or higher. The dosing was similar to the GAUSS-2 trial, except evolocumab was compared to placebo alone as shown in the following groups:

Group 1: Evolocumab 140 mg subcutaneous injection every two weeks.
Group 2: Evolocumab 420 mg subcutaneous injection every month.
Group 3: Subcutaneous injection of placebo every two weeks.
Group 4: Subcutaneous injection of placebo every month.

The primary endpoints were percentage change in plasma LDL-C from baseline to the mean of weeks 10 and 12, and to week 12. At the mean of weeks 10 and 12, patients in group 1 saw a mean reduction in LDL-C of 60.2 percent ($p < 0.0001$). Group 2 saw a mean reduction of LDL-C levels of 65.6 percent ($p<0.0001$). Also, rates of adverse events were similar to those seen in previous studies of evolocumab. Investigators did not see any serious adverse events that led to discontinuation of the study drug.

Evolocumab received additional approval for use in HoFH due to results from Trial Evaluating PCSK9 Antibody in Subjects with LDL-C Receptor Abnormalities (TESLA).[6] The ongoing trial Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) will provide additional information regarding the long-term efficacy of evolocumab plus statin therapy, and its overall impact on cardiovascular risks.[17]

Impact on Healthcare

Long-term data on the effects of PCSK9 inhibitors is several years away, but there is reason to believe that lowering patient LDL-C levels will improve a broad range of cardiovascular outcomes. Despite increasing research in the area, high cholesterol remains one of the largest nationwide health concerns with reports as recent as 2010 estimating that nearly 57 million adults in the United States have hypercholesterolemia.[18] The PCSK9 inhibitors will likely serve as efficacious adjuncts to statin therapy for those with FH or ASCVD. Furthermore, these drugs may potentially be useful as monotherapy for patients who cannot use or tolerate statins. While some patients may be deterred by having to inject the medication, these agents are proposed as high-compliance formulations. Two administrations per month from autoinjectors or prefilled syringes may be sufficient for therapy.[19,20]

Yet, there are numerous challenges healthcare professionals may face as they try to provide these medications to their patients. One of the greatest barriers to accessing PCSK9 inhibitors is cost. Upon approval of alirocumab, Sanofi-Regeneron announced a wholesale acquisition cost (WAC) of $40 a day, or $14,600 a year.[5,19] Subsequent approval of the competitor, evolocumab, was projected to considerably reduce the price of alirocumab, but Amgen announced the WAC at $14,100 a year.[20] Although the WAC does not include discounts or rebates, and serves merely as an estimate of the manufacturer's list price, each drug has entered the market well beyond its projected annual costs of $7,000 to $12,000.[19] Pharmacy benefit managers note that unlike many monoclonal antibodies used for terminal or curable diseases, PCSK9 inhibitors are currently indicated for indefinite use, and future pending studies could see routine use as a replacement for statins.[20] Approximately 71 million Americans at least 20 years of age have LDL-C levels that are borderline high or greater (>130 mg/dL).[18] Millions more have a history of coronary artery disease or previous cardiac event, suggesting that a wide range of patients beyond those with FH and ASCVD may benefit from PCSK9 inhibitors. Therefore, high healthcare costs may be a consequence of these medications if prices remain elevated.

Role of the Pharmacist

With the emergence of PCSK9 inhibitors, pharmacists have many opportunities for patient education. Patients prescribed these medications should be educated on proper aseptic and subcutaneous injection technique and disposal of used drug delivery devices. The most common adverse events leading to discontinuation in clinical trials included general allergic reactions, elevated liver enzymes and neurocognitive events. Other minor side effects include pain or irritation at the site of injection as well as flu-like symptoms. Patients should be counseled that rotating injection sites may help reduce skin irritation. As with all monoclonal antibodies, there is a potential for immunogenicity. Praluent® (alirocumab) and Repatha® (evolocumab) syringes should be stored under refrigeration and allowed to warm at room temperature approximately 30 minutes before use.[21,22] All storage, packaging and patient information provided by the manufacturers should be closely followed.

Additionally, pharmacy benefit managers that pay for these high-priced pharmaceuticals want evidence of efficacy and patient compliance to justify the use of PCSK9 inhibitors. They will likely require regular patient follow-up visits with

their prescriber and routine monitoring to determine baseline LDL-C levels. Pharmacists can assist patients in managing trips to multiple physicians, adherence to a list of medications and maintaining necessary lifestyle modifications. Engaging patients in comprehensive medication reviews and medication therapy management services will further improve adherence rates and overall patient outcomes.[23]

Patient assistance programs are currently available for those seeking financial support to cover the costs of these medications. Pharmacists can help patients acquire this information online at www.praluenthcp.com and www.repathahcp.com or by calling the support phone lines listed on each website.

Conclusion

The PCSK9 Inhibitors are a novel and highly efficacious class of lipid-lowering medications. These monoclonal antibodies facilitate the removal of LDL-C from the blood and have demonstrated superior changes from baseline compared to both placebo and standard lipid-lowering therapy. Neither alirocumab nor evolocumab are approved as monotherapy or first-line therapy, and trials on long-term cardiovascular outcomes are ongoing. While they have been on the market for only a few months, there is already much debate regarding the high financial costs and potential ramifications of these increasingly prescribed drugs. Despite this, the PCSK9 inhibitors present a new and efficacious pharmacotherapeutic option for patients with hypercholesterolemia.

References

1. Robinson JG, Farnier M, Kremf M, Bergeron J, Luc G, Averna M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med.* 2015 Apr 16;372(16):1489-1499.
2. Stoes E, Colquhoun D, Sullivan D, Civeira F, Rosenson RS, Watts GF, et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance. *J Am Coll Cardiol.* 2014 Jun 17;63(23):2541-2548.
3. Poirier S, Mayer G, Poupon V, McPherson PS, Desjardins R, Ly K, et al. Dissection of the endogenous cellular pathways of PCSK9-induced low density lipoprotein receptor degradation. *J Biol Chem.* 2009 Jul 27; 284 (42): 28856-28864.
4. Saavedra YGL, Zhang J, Seidah NG. PCSK9 prosegment chimera as novel inhibitors of LDLR degradation [Internet]. *PLoS ONE.* 2013 Aug [cited 2015 Sep 6]; 8(8):1-9. Available from: journals.plos.org/plosone/article?id=10.1371/journal.pone.0072113.
5. Regeneron and Sanofi announce FDA approval of Praluent® (alirocumab) injection, the first PCSK9 inhibitor in the US, for the treatment of high LDL cholesterol in adult patients [news release]. Paris, France and Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; 2015 Jul 24. Available from: newsroom.regeneron.com/releasedetail.cfm?ReleaseID=923788. Accessed 2015 Sep 6.
6. FDA approves Repatha to treat certain patients with high cholesterol [news release]. Silver Spring (MD): US FDA; 2015 Aug 27. Available from: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm460082.htm. Accessed 2015 Sep 6.
7. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/ American Heart Association task forces on practice guidelines. *J Am Coll Cardiol* [Internet]. 2014 Jul 1 [cited 2015 Sept 6]; 63(25 Part B):2889-2934. Available from: www.guideline.gov/content.aspx?id=48337&search=familial+hypercholesterolemia.
8. Lexicomp [Internet]. Hudson (OH): Lexicomp Inc. 1978-2015. Ezetimibe, Pharmacology; [Updated 2015 Oct 2; cited 2015 Oct 3]; [1 screen]. Available from: online.lexi.com/.
9. Robinson JG. Management of familial hypercholesterolemia: a review of the recommendations from the national lipid association expert panel on familial hypercholesterolemia. J Manag Care Pharm. 2013 Mar; 19 (2):139-149.
10. Lexicomp [Internet]. Hudson (OH): Lexicomp Inc. 1978-2015. Lomitapide, Pricing: US; [Updated 2015 Oct 14; cited 2015 Nov 5]; [1 screen]. Available from: online.lexi.com/.
11. Lexicomp [Internet]. Hudson (OH): Lexicomp Inc. 1978-2015. Mipomersen, Pricing: US; [Updated 2015 Sep 3; cited 2015 Nov 5]; [1 screen]. Available from: online.lexi.com/.
12. Lexicomp [Internet]. Hudson (OH): Lexicomp Inc. 1978-2015. Evolocumab, Pricing: US; [Updated 2015 Aug 10; cited 2015 Nov 5]; [1 screen]. Available from: online.lexi.com/.
13. Lexicomp [Internet]. Hudson (OH): Lexicomp Inc. 1978-2015. Alirocumab, Pricing: US; [Updated 2015 Jul 27; cited 2015 Nov 5]; [1 screen]. Available from: online.lexi.com/.
14. ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Institutes of Health. NCT01663402, ODYSSEY Outcomes: evaluation of cardiovascular outcomes after an acute coronary syndrome during treatment with alirocumab; [updated 2015 Oct 25; cited 2015 Nov 5]; [about 4 screens]. Available from: clinicaltrials.gov/ct2/show/NCT01663402.
15. U.S. Food and Drug Administration. [Internet]. Silver Spring (MD): FDA. FDA approves Praluent to treat certain patients with high cholesterol; 2015 Jul 24 [2015 Jul 24; cited 2015 Sep 10]; [about 2 screens]. Available from: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm455883.htm.
16. Raal FJ, Stein EA, Doufour R, Turner T, Civeira F, Burgess L, Langslet G, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2015 Jan 24;385(9965):331-340.
17. U.S. Food and Drug Administration. [Internet]. Silver Spring (MD): FDA. FDA approves Repatha to treat certain patients with high cholesterol; 2015 Aug 27 [2015 Aug 27; cited 2015 Sep 10]; [about 2 screens]. Available from: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm460082.htm.
18. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation.* 2014;129: e28-e292.
19. Shrank W, Lotvin A, Singh S, Brennan T. Health Affairs Blog [blog on the Internet]. Millwood (VA): Project HOPE: The People-to-People Health Foundation, Inc. 1995-2015. In the debate about cost and efficacy, PCSK9 inhibitors may be the biggest challenge yet; 2015 Feb 17 [cited 2015 Oct 16]; [about 4 screens]. Available from: healthaffairs.org/blog/2015/02/17/in-the-debate-about-cost-and-efficacy-pcsk9-inhibitors-may-be-the-biggest-challenge-.yet/.
20. Caffrey MK. For now, PBMs just say no to high-cost PCSK9 inhibitors. *Am J Manag Care.* 2015 Sep;21(13):456-457.
21. Praluent® (alirocumab) injection [package insert]. Tarrytown, NY/ Bridgewater, NJ: Regeneron Pharmaceuticals, Inc./sanofi-aventis U.S. LLC; 2015 Jul. products.sanofi.us/praluent/praluent.pdf.
22. Repatha(R (evolocumab) injection [package insert]. Thousand Oaks, CA: Amgen Inc.; 2015 Sep. Available from: pi.amgen.com/united_states/repatha/repatha_pi_hcp_english.pdf.
23. Specialty Pharmacy Times [Internet]. Plainsboro Township, NJ: Intellisphere, LLC; 2006-2015. PCSK9 inhibitors: smoothing the path to access and value; 2015 Oct 12 [cited 2015 Oct 26]; [about 3 screens]. Available from: www.specialtypharmacytimes.com/publications/specialty-pharmacy-times/2015/October-2015/PCSK9-Inhibitors-Smoothing-the-Path-to-Access-and-Value.

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Assessment Questions

1. To what does proprotein convertase subtilisin/kexin type 9 bind?
   A. Epidermal growth factor domain A
   B. Low density lipoprotein cholesterol
   C. Hepatocyte membrane
   D. Apolipoprotein B-100

2. Inhibition of proprotein convertase subtilisin/kexin type 9 leads to increased recycling of _____?
   A. cholesterol
   B. triglycerides
   C. low density lipoprotein receptor
   D. hepatocytes

3. Alirocumab (Praluent®) is FDA approved to treat which conditions?
   A. Familial hypercholesterolemia
   B. Atherosclerotic cardiovascular disease
   C. Hypertension
   D. Both A and B

4. What is an additional approved indication for evolocumab (Repatha®)?
   A. Homozygous Familial Hypercholesterolemia
   B. Heterozygous Familial Hypercholesterolemia
   C. Clinical atherosclerotic cardiovascular disease
   D. Monotherapy treatment of hypercholesterolemia

5. What new information not addressed in completed clinical trials of PCSK9 inhibitors will be provided by the FOURIER and ODYSSEY OUTCOMES trials?
   A. Safety data
   B. Cardiovascular risk reduction data
   C. Efficacy of PCSK9 inhibitors with concomitant statin therapy
   D. Adverse effects when co-administered with ezetimibe

6. Which side effects were observed at a higher rate in the treatment group versus placebo group in the ODYSSEY LONG TERM trial?
   A. Myalgia and nausea
   B. Myalgia, neurocognitive effects and ophthalmologic events
   C. Injection site reactions, allergic reactions and GI upset
   D. Anaphylaxis requiring study discontinuation

7. Of the following options, which is the greatest barrier in preventing patient access to PCSK9 inhibitors?
   A. Compliance issues
   B. Lack of drug effectiveness data
   C. High medication costs
   D. Low product supply

8. Which of the following is an advantage to therapy with PCSK9 inhibitors?
   A. It is approved as monotherapy for patients with familial hypercholesterolemia.
   B. Dosing is once or twice monthly, which could improve adherence.
   C. Marked decreases in low density lipoprotein cholesterol for most patients.
   D. Both B and C.

9. What is a concern associated with long-term administration of monoclonal antibodies such as alirocumab (Praluent®) and evolocumab (Repatha®)?
   A. Immunogenicity
   B. A paradoxical increase in low density lipoprotein cholesterol
   C. Poor drug bioavailability
   D. Complex dosing regimens

10. Which of the following is an important step in the administration of alirocumab (Praluent®)?
    A. Keep injector pen frozen until ready to use.
    B. Patients should be counseled on proper intramuscular administration.
    C. Allow pen or syringe to warm at room temperature for 30 minutes prior to administration.
    D. Thoroughly shake the pen or syringe prior to use.

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