New Drug Update

Alirocumab—a novel drug for familial hypercholesterolemia

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Abstract

Familial hypercholesterolemia (FH) is a genetically transmitted condition, wherein abnormally high levels of total cholesterol and low density lipoproteins (LDL) are seen. Occurrence of premature cardiovascular complications is common, resulting in significant morbidities and fatalities. Currently statins are the first-choice drugs to treat FH, given alone, or in combination with other lipid lowering drugs. Alirocumab is a monoclonal antibody directed against PCSK9, a 'gain-of-function' mutation of which is thought to be responsible for the defective processing of LDL cholesterol, resulting in lesser uptake of LDL-C into the hepatocytes. It was approved by the US-FDA in July 2015 as a *first-in-class* drug, "for use in addition to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH) or patients with clinical atherosclerotic cardiovascular disease such as heart attacks or strokes, who require additional lowering of LDL cholesterol." It has to be administered subcutaneously every 2 weeks, and the dose is titrated as per need. Injection-site reactions, myalgia, neurocognitive events, pruritus were the major adverse effects observed during clinical trials. Inhibition of PCSK 9 is a new promising target for the treatment of patients with familial hypercholesterolemia.

KEY WORDS: Alirocumab; familial hypercholesterolemia; PCSK 9 inhibition

Introduction

Familial hypercholesterolemia (FH) is a genetically transmitted condition, wherein abnormally high levels of total cholesterol and low density lipoproteins (LDL) are seen. Patients with FH are known to develop aggressive and premature cardiovascular complications, increasing their likelihood of developing significant morbidities and fatalities.[1] The inheritance is autosomal dominant, and along with marked hypercholesterolemia,xanthomas are noted commonly on the Achilles tendons and metacarpal phalangeal extensor tendons of the hands of patients with untreated FH.[2]

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Pathophysiology of Familial Hypercholesterolemia

FH can be either homozygous (HoFH), which is the most severe variety where there are mutations in both the alleles of the gene, or the more common heterozygous (HeFH) variety, where a single mutation is present, and is less severe than HoFH. Proprotein convertase subtilisin/kexin Type 9 (PCSK9) is one among the mutations that are known to play a role, and is inherited in an autosomal dominant manner. PCSK9 has now merged as a new target for therapy in FH.[2]

Current Approach to Management

The target of treatment in FH was to reduce the LDL cholesterol levels to below 130 mg/dL, or a 50% reduction from the baseline levels.[3] Earlier, bile acid sequestrants were considered as the first choice therapy, especially in children, due to the lack of systemic uptake of these drugs. However, the efficacy being modest when compared to statins, these drugs gradually fell out of use as first-line drugs, and are now used

in combination with statins. Currently, statins (3-hydroxy-3methyl-glutaryl-CoA reductase inhibitors) are the first choice of drugs to treat HeFH.[3,4] Ezetimibe, a first-in-class drug that prevents cholesterol absorption in the small intestine, is used either in combination with statins or alone in statin-intolerant patients.[3–5] The response to therapy is variable, and the fall in LDL cholesterol may not be very high in patients with HoFH. However, a reduction in cardiovascular events and mortality has been observed with the use of statins in these patients.[6] Newer therapeutic options include mipomersen—an antisense oligonucleotide that targets the mRNA coding for a poB-100, PCSK9 inhibitors, lomitapide—inhibits the microsomal triglyceride transfer protein (MTP), which helps in the transfer of triglycerides to apolipoprotein B and thereby in the production of LDL cholesterol.[3] In this review, we aim to explore the therapeutic role of alirocumab, amonoclonal antibody directed against PCSK9.

What is Pcsk9?

PCSK9 (proprotein convertase subtilisin/kexin Type 9) belongs to the serine protease family, and aids in the activation/inactivation of other enzymes, growth factors, etc. In FH, a "gain-of-function" mutation affecting PCSK9 is thought to be responsible for its defective processing and functioning.[7] It binds to the LDL receptor (LDL-R) and promotes its intracellular lysosomal degradation via uptake into the hepatocytes. This results in slower recycling of the LDL receptor, and thereby, lesser uptake of LDL into the cell.[8] This target may also play a role in those patients who require intensive control of LDL cholesterol.

Currently, different approaches to inhibit PCSK9 have emerged, including *gene silencing* by the use of antisense oligonucleotides and small interfering RNA (siRNA); *mimetic peptides* that mimic PCSK9 to bind to the LDL-R; small molecule inhibitors; and *monoclonal antibodies* including alirocumab, evolocumab, and bococizumab.[7]

Alirocumab

Alirocumab (formerly SAR236553/REGN727) is a fully human monoclonal antibody against PCSK9, and prevents it from acting on the LDL-R to bring about its degradation.[9] It was approved by the US-FDA in July 2015 as a first-in-class drug, "for use in addition to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH) or patients with clinical atherosclerotic cardiovascular disease such as heart attacks or strokes, who require additional lowering of LDL cholesterol." The approval followed evaluation of the drug in five phase 3, double-blind, placebo-controlled trials that involved 2476 participants who received alirocumab.[10]

Through the Developmental Pipeline

Preclinical Phase: A trial conducted in mice and nonhuman primates, to study the effects of a PCSK9 neutralizing antibody on the LDL cholesterol levels, demonstrated significant LDL lowering effects. Both wild-type and genetically engineered mice ($LDLR^{-/-}$, those mice without LDL receptors and with markedly high LDL levels) were used in the study, and the LDL lowering effect was not observed in the $LDLR^{-/-}$ type mice, implicating the requirement of an intact LDL receptor for the beneficial effect. This effect was also observed in Cynomolgus monkeys, wherein a single dose of the antibody was seen to produce an 80% reduction in the LDL cholesterol levels, and the effect was seen to be maintained for 10 days following the dose.[11]

Clinical Trials: Three phase 1 trials were carried out in both healthy volunteers (two randomized, single ascending-dose studies) and in patients with familial or nonfamilial hypercholesterolemia (one randomized, placebo-controlled, multiple-dose trial), demonstrated no discontinuation of the drug due to adverse events. The principal secondary outcome to look at the effect of REGN727 on the lipid profile, showed a significant fall in LDL levels in both sets of patients.[12] An open-label, randomized, phase 1 study was conducted in healthy subjects (18–45 years of age) with LDL cholesterol levels >95 mg/dL, with different sites of injection (abdomen, upper arm, or thigh) of a single dose of alirocumab 75 mg. The dose was tolerated well, and both pharmacokinetics as well as pharmacodynamics were similar when the drug was given at the three sites, which implicated that alirocumab could be given interchangeably at any of the three sites.[13]

In a phase 2 trial (multicenter, randomized, placebo-controlled), conducted in adults with HeFH,the subjects received REGN727 150, 200, or 300 mg every 4 weeks, or 150 mg every 2 weeks, or placebo every 2 weeks (in addition to statin, with or without ezetimibe). Along with the drug being well-tolerated, a substantial lowering of LDL cholesterol was observed.[14] Another phase 2 trial (multicenter, double-blind, placebo-controlled) that studied the effect of addition of SAR236553 to the statin dose, showed similar significant LDL cholesterol lowering effect.[15]

Three of the phase three trials, referred to as the ODYSSEY phase 3 trials, were multicenter, multinational, randomized, double-blind, placebo-controlled studies; the patients were randomized in 2:1 ratio to either the alirocumab or the placebo-groups. The studies were aimed at studying the efficacy and long-term safety of alirocumab as a treatment option in patients with HeFH.[16] The other two studies, referred to as ODYSSEY OPTIONS studies (OPTIONS I & II studies), were designed along similar lines and the key difference being OPTIONS I included patients specifically on atorvastatin at baseline with/without the addition of ezetimibe, and OPTIONS II included patients on rosuvastatin at baseline, again with/without the addition of ezetimibe.[17]

The first report from the ODYSSEY studies, dubbed the ODYSSEY MONO study wherein a comparison was made between

alirocumab and ezetimibe, was given at the end of 24 weeks, and it was observed that alirocumab showed a significantly higher LDL cholesterol lowering capacity than ezetimibe.[18] The ODYSSEY LONG TERM trial included 2341 patients of which 1553 received alirocumab (150 mg every 2 weeks) and 788 received placebo, in addition to statin therapy. It was observed that over the 78-week study period, addition of alirocumab to maximum tolerated statin therapy produced a significant reduction in LDL cholesterol levels. A post hoc analysis also showed a decrease in the rate of cardiovascular events among patients that received alirocumab.[19,20]

The results from the other two studies, the ODYSSEY FHI and FHII, also showed similar results wherein a significant lowering of LDL cholesterol levels was observed with alirocumab. Here, alirocumab was initially started at a dose of 75 mg every 2 weeks, increased to 150 mg if the LDL cholesterol at the 8th week was ≥1.8 mmol/L (70 mg/dL). The fall in LDL cholesterol was observed to be maintained throughout the 78-week study period.[21] Also, other modified studies in the same program, coded as ODYSSEY COMBO I and COMBO II, showed alirocumab to have similar therapeutic advantage.[22,23] Results from the ODYSSEY ALTERNATIVE study, which was designed to evaluate the efficacy and safety of alirocumab, in patients with well-documented statin intolerance, are yet to be published.[24] The ODYSSEY OPTIONS studies also demonstrated a favorable outcome with alirocumab over doubling the atorvastatin dose or addition of ezetimibe or even switching over to rosuvastatin.[25]

Adverse Effects: Injection-site reactions, myalgia, neurocognitive events (amnesia, memory impairment, confusional state), pruritus, ophthalmologic events were the adverse effects that were observed in patients receiving alirocumab across the studies. Amnesia, memory impairment, and a state of confusion were the neurocognitive events that occurred. However, these did not classify as being 'serious' adverse events. Patients developed anti-drug antibodies across studies, but a reduction in the response to treatment with alirocumab was seen in one patient in one phase 3 study. No other specific safety issue was observed in these patients who were positive for antidrug antibody.[20-22,25] Elevated alanine amino-transaminase was observed in a few patients in one of the phase 3 studies.[23]

Recommended Dose and Regimen: It is marketed as a single-dose prefilled syringe/pen for injection, in strengths of either 75 mg/mL or 150 mg/mL. The recommended initial dose is 75 mg subcutaneously every 2 weeks, which can be increased to 150 mg/mL every 2 weeks, if the response (decrease in LDL cholesterol) is inadequate.[19]

Current Status of Alirocumab

Currently, of all the conventional drugs available to treat hypercholesterolemia, statins bring about the maximum reduction in LDL cholesterol levels. However, this effect is not seen in patients with familial hypercholesterolemia, especially in those patients with HoFH.[26] The first statin (lovastatin) was approved in 1987, on the basis of its effect in reduction of LDL cholesterol. In the approval process of alirocumab, the same end point was used as a surrogate measure of its clinical benefit.[27] A powered meta-analysis of the safety and efficacy of PCSK9 inhibitors (both alirocumab and evolocumab) that included 25 randomized controlled trials, concluded that both drugs were safe, tolerated well, and brought about favorable changes in the lipid profile.[28]

The NICE guidelines for the identification and management of FH recommends the initial use of statins, followed by the addition of ezetimibe if statin monotherapy is ineffective, along with dietary and lifestyle modifications. More often than not, treatment once started has to be continued for life.[29] Long term use of statins is associated with adverse effects such as hepatotoxicity and myopathy[26] Ezetimibe monotherapy affords a maximum effect of about 15–20% fall in LDL cholesterol levels, and hence is usually used in combination with statins.[26]

Alirocumab by the inhibition of PCSK9, offers a new target, and hence a new ray of hope for patients with familial hypercholesterolemia especially in people with atherosclerosis who require additional lowering of LDL cholesterol when diet and statin treatment have not worked. However, subcutaneous injections and the added health-care costs, as alirocumab is currently priced at US$40 per day (which comes to US$14,600 per year), can appear as a severe drawback to achieve patient compliance.[30] Moreover, its long term safety profile and evidence of its effectiveness in preventing death and morbidity due to cardiovascular causes over a prolonged time in these patients is yet lacking and warrants further trials. This drug is not yet approved in India; owing to an unmet medical need, clinical trials are expected to begin soon. ODYSSEY OUTCOMES, a phase 3 cardiovascular outcomes trial that will enroll about 18,000 patients and evaluate the effect of alirocumab on the occurrence of cardiovascular event might shed more light on this newer avenue for patients with FH.

References

1. Austin MA, Hutter CM, Zimmern RL, Humphries SE. Familial hypercholesterolemia and coronary heart disease: a HuGE association review. Am J Epidemiol 2004;160:421–9.
2. Blom DJ. Familial hypercholesterolaemia. JEMDSA 2011;16(1): 17–24.
3. Varghese MJ. Familial hypercholesterolemia: a review. Ann Pediatr Card 2014;7:107–17.
4. Hovingh GK, Davidson MH, Kastelein JJP, O'Connor AM. Diagnosis and treatment of familial hypercholesterolaemia. Eur Heart J 2013;34:962–71.
5. Robinson JG. Management of familial hypercholesterolemia: areview of the recommendations from the National Lipid Association Expert Panel on familial hypercholesterolemia. J Manag Care Pharm 2013;19(2):139–49.
6. Farniera M, Bruckert E. Severe familial hypercholesterolaemia: current and future management. Arch Cardiovas Dis 2012;105:656–65.
7. Pitts RN, Eckel RH. The emerging role of PCSK9 inhibitors in preventive cardiology. EurCardiol Rev 2014;9(2):65–70.

8. Gencera B, Lambert G, Mach F. PCSK9 inhibitors. Swiss Med Wkly 2015;145:w14094.
9. Kühnast S, van der Hoorn JWA, Pieterman EJ, van den Hoek AM, Sasiela WJ, Gusarova V, et al. Alirocumab inhibits atherosclerosis, improves the plaque morphology, and enhances the effects of a statin. J Lipid Res 2014;55:2103–12.
10. Fda.gov [Internet]. *Maryland: US Food and Drug Administration*; [updated 2015 July 24, cited Nov 19, 2015]. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm455883.htm.
11. Chan JCY, Piper DE, Cao Q, Liu D, King C, Wang W,et al. A proprotein convertase subtilisin/kexin type 9 neutralizing antibody reduces serum cholesterol in mice and nonhuman primates. ProcNatlAcadSci USA 2009;106:9820–5.
12. Stein EA, Mellis S, Yancopoulos GD, Stahl N, Logan D, Smith WB, et al. Effect of a monoclonal antibody to PCSK9 on LDL cholesterol. N Engl J Med 2012;366(12):1108–18.
13. Lunven C, Paehler T, Poitiers F, Brunet A, Rey J, Hanotin C, et al. A randomized study of the relative pharmacokinetics, pharmacodynamics, and safety of Alirocumab, a fully human monoclonal antibody to PCSK9, after single subcutaneous administration at three different injection sites in healthy subjects. Cardiovasc Ther 2014;32:297–301.
14. Stein EA, Gipe D, Bergeron J, Gaudet D, Weiss R, Dufour R, et al. Effect of a monoclonal antibody to PCSK9, REGN727/ SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial. Lancet 2012;380:29–36.
15. Roth EM, McKenney JM, Hanotin C, Asset G, Stein EA. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. N Engl J Med 2012;367:1891–900.
16. Kastelein JJP, Robinson JG, Farnier M, Krempf M, Langslet G, Lorenzato C, et al. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia not adequately controlled with current lipid-lowering therapy: design and rationale of the ODYSSEY FH studies. Cardiovasc Drugs Ther 2014;28:281–9.
17. Robinson JG, Colhoun HM, Bays HE, Jones PH, Du Y, Hanotin C, et al. Efficacy and safety of alirocumab as add-on therapy in high-cardiovascular-risk patients with hypercholesterolemia not adequately controlled with atorvastatin (20 or 40 mg) or rosuvastatin (10 or 20 mg):design and rationale of the ODYSSEY OPTIONS studies. Clin Cardiol 2014;37(10):597–604.
18. Roth EM, Taskinen M, Ginsberg HN, Kastelein JJP, Colhoun HM, Robinson JG, et al. Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: results of a 24 week, double-blind, randomized phase 3 trial. Int J Cardiol 2014;176:55–61.
19. Regeneron.com [Internet]. *New York: Regeneron Pharmaceuticals, Inc*.; [updated 2015 July, cited Nov 19, 2015]. Available at: http://www.regeneron.com/Praluent/Praluent-fpi.pdf.
20. Robinson JG, Farnier M, Krempf 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;372(16):1489–99.
21. Kastelein JJP, Ginsberg HN, Langslet G, Hovingh GK, Ceska R, Dufour R, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. Eur Heart J 2015;36:2996–3003.
22. Kereiakes DJ, Robinson JG, Cannon CP, Lorenzato C, Pordy R, Chaudhari U, et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: the ODYSSEY COMBO I study. Am Heart J 2015;169(6):906–15.
23. Cannon CP, Cariou B, Blom D, McKenney JM, Lorenzato C, Pordy R, et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBOII randomized controlled trial.Eur Heart J 2015;36:1186–94.
24. Moriarty PM, Jacobson TA, Bruckert E, Thompson PD, Guyton JR, Baccara-Dinet MT, et al. Efficacy and safety of alirocumab, a monoclonal antibody to PCSK9, in statin-intolerant patients: design and rationale of ODYSSEY ALTERNATIVE, a randomized phase 3 trial. JClinLipidol 2014;8:554–61.
25. Bays H,Gaudet D,Weiss R, Ruiz JL, Watts GF, Gouni-Berthold I, et al. Alirocumab as add-on to atorvastatin versus other lipid treatment strategies: ODYSSEY OPTIONS I Randomized Trial. J Clin Endocrinol Metab 2015;100(8):3140–8.
26. Bersot TP. Drug therapy for hypercholesterolemia and dyslipidemia: introduction. In: Brunton LL, Chabner BA, Knollmann BC (Eds.), *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 12th ed. New Delhi: McGraw-Hill, 2011. pp. 876–904.
27. Everett BM, Smith RJ, Hiatt WR. Reducing LDL with PCSK9 inhibitors—the clinical benefit of lipid drugs. N Engl J Med 2015;373(17):1588–91.
28. Zhang X, Zhu Q, Zhu L, Chen J, Chen Q, Li G, et al. Safety and efficacy of anti-PCSK9 antibodies: a meta-analysis of 25 randomized, controlled trials. BMC Med 2015;13:123.
29. Nice.org.uk [Internet]. *London: National Institute for Health and Care Excellence*; [updated 2008 August 27, cited 2015 Nov 19]. Available at: https://www.nice.org.uk/guidance/cg71/resources/familial-hypercholesterolaemia-identification-and-management-975623384005.
30. Sanofi and Regeneron Announce FDA Approval of Praluent® (Alirocumab) Injection, the First PCSK9 Inhibitor in the US, for the Treatment of High LDL Cholesterol in Adult Patients. [updated July 24, 2015. cited March 17, 2016]. Available at: http://en.sanofi.com/NasdaQ_OMX/local/press_releases/sanofi_and_regeneron_announce__1941221_24-07-2015!21_24_28.aspx#

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