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EDITORIAL
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PCSK-9 INHIBITORS

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Hyperlipidemia (elevated levels of LDL-C) is a well-known risk factor of cardiovascular diseases (CVD). Statins are well known and proven drugs for the lipid management of individuals at increased risk for developing CVD events[1]. However, the patients who are either intolerant to statin therapy, develop CVD despite being on maximally tolerated statin therapy, or have severe hypercholesterolemia i.e familial hypercholesterolemia had limited options. Recently the Food and Drug Administration (FDA) approved two medications (PCSK-9 inhibitors) which act on a novel pathway to reduce LDL-C levels in blood.

HOW DO PCSK9 INHIBITORS WORK?

PCSK-9 inhibitors are monoclonal antibodies which inactivate proprotein convertase subtilsin-kexin type 9 (PCSK9). The PCSK9 protein has a strong inhibitory action on recycling of the LDL receptor (LDLR). PCSK-9 protein is predominantly produced by hepatocytes, with other sites being kidneys and intestines.[2,3] On the surface of liver cell, LDL receptor binds to LDL and the LDLR–LDL complex is then internalized, after which the LDLR is normally recycled back to the cell surface up to 150 times.[4] The role of PCSK9 protein is that it binds to the LDLR on the surface of the hepatocyte, causing internalization and degradation of the LDL receptor in the lysosomes, this process in turn reduces the number of LDL receptors on the cell surface. So, by Inhibition of PCSK9, number of available LDL receptors on the cell surface is increased and uptake of LDL-C into the cell is augmented. PCSK9 inhibition thus offers a novel therapeutic approach for the lowering of LDL-C levels.[5] Currently, the only FDA-approved PCSK9 inhibitors are two fully human monoclonal antibodies that bind extracellular PCSK9: alirocumab[6] and evolocumab.[7]

FDA APPROVAL STATUS OF PCSK9 INHIBITORS AND REDUCTION IN LDL-C:

Alirocumab (Praluent) was approved by FDA in July 2015 for adult patients with heterozygous familial hypercholesterolemia or in patients with clinically significant atherosclerotic CVD requiring additional LDL lowering despite being on diet control and maximally tolerated statin therapy. Alirocumab's long-term safety and efficacy was evaluated in ODYSSEY trials which include CHOICE I, CHOICE II, OLE, LONG TERM, COMBO I, COMBO II, FH I, FH II, HIGH FH, MONO, ALTERNATIVE, OPTIONS I and OPTIONS II. There was a 65% reduction in LDL-C levels in a dose dependent fashion at maximal doses.[8]

FDA also approved Evolocumab (Repatha) in August, 2015 for use in adult patients with homozygous familial hypercholesterolemia, heterozygous familial hypercholesterolemia, or clinical atherosclerotic CVD requiring additional lowering of LDL cholesterol despite being on a controlled diet and maximally-tolerated statin therapy. PROFICIO (Program to reduce LDL-C and cardiovascular outcomes following inhibition of PCSK9 in different populations) phase III 14 trials were designed to evaluate efficacy and long-term safety of evolocumab. Every two-week regimen reduced LDL-C levels by up to 65% as compared to approximately 50% with every 4-wk regimen.

DOSAGE:

Alirocumab (Praluent): 75-150 mg every two weeks
Evolocumab (Repatha): 140 mg every two weeks or 420 mg monthly

ADVERSE EFFECTS:

The most common adverse effects observed with Alirocumab include nasopharyngitis, erythema, itchiness, swelling, pain or tenderness, influenza, urinary tract infection, diarrhea, bronchitis, myalgia, muscle spasms, sinusitis and cough. The most common adverse effects of Evolocumab include nasopharyngitis, upper respiratory tract infection, back pain and nausea. A small percentage (2.4%) of some serious cardiac adverse events were also noted which include palpitations, angina pectoris, and ventricular premature contractions.

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