PCSK9 inhibition – Ready for prime time?

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Proprotein convertase subtilisin-kexin type 9 (PCSK9) is a glycoprotein that promotes the destruction of LDL cholesterol receptors in the liver. Thus, high levels of PCSK9 result in reduced activity of LDL receptors in the liver and higher LDL cholesterol levels. Conversely, loss of function mutations in PCSK9 results in lower LDL cholesterol and is associated with a reduction in coronary events.

Two commercially available monoclonal antibodies to PCSK9, alirocumab and evolocumab, have been developed. Evidence of the lipid-lowering efficacy of these agents has been robust,[2] and evidence of clinical cardiovascular event reduction has begun to arrive.

Through 2016, the available data included prespecified but exploratory analyses of two open-label randomized extension studies. The OSLER clinical trial program evaluated evolocumab, and the ODYSSEY LONG TERM trial evaluated alirocumab, each studied against a background of statin therapy. Both trials showed a reduced incidence of major cardiovascular events with the active PSCK9 inhibitor therapy, though the total number of events was small.[3,4] In both studies, the event reduction was found via post-hoc analysis, and neither trial was powered to detect a difference in clinical ASCVD events.

The FOURIER trial, published in early 2017, is a randomized study of the addition of evolocumab, in either of its two clinical dosing regimens (140 mg s.c. every two weeks or 420 mg s.c. monthly) added to a background of optimized statin therapy. The trial was appropriately powered to assess clinical cardiovascular events, with over 13,000 patients enrolled in each group. Both groups were well-treated by traditional lipid criteria, with a median baseline LDL-C of 92 mg/dl. The addition of evolocumab lowered LDL-C by an additional 59% at 48 weeks with a median on-treatment LDL-C of 30 mg/dl in the active treatment arm. The primary end point, a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization, was reduced by 15% over the median duration of follow-up of 26 months. The prespecified secondary endpoint, the "harder" components of the primary endpoint—a composite of cardiovascular death, myocardial infarction, or stroke—was reduced by 20%. And the benefits of evolocumab therapy appeared to increase over time, with a 25% reduction in the secondary endpoint after the first year.[5]

Cardiovascular death was not reduced with evolocumab therapy, however. Cause for concern? Perhaps not. Most cardiovascular event trials of lipid-lowering therapies have included much longer subject follow up, around five years. And in many of those trials, CV death benefit did not emerge until after two years of active treatment.[6-12]

Early in the PCSK9 clinical trial development programs, some concern arose as to whether the very low on-treatment LDL levels achieved by PCSK9 inhibitor therapy would lead to a decline in neurocognitive function.[13] In the EBBINGHAUS study, an objective assessment of neurocognitive function in nearly 2,000 patients enrolled in the FOURIER trial, no decline in neurocognitive function was found with evolocumab therapy.[14]

The FOURIER trial population included patients with clinical atherosclerotic cardiovascular disease, and additional characteristics placed them at increased cardiovascular risk. A slightly different patient population is being studied in the ongoing ODYSSEY

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Table. PCSK9 Inhibitor Clinical Trials

Trial Name	FOURIER	ODYSSEY OUTCOMES	SPIRE 1 & 2	ORION-1
Agent	Evolocumab	Alirocumab	Bococizumab	Inclisiran
Mechanism of Action vs. PCSK9	Human monoclonal antibody	Human monoclonal antibody	"Humanized" monoclonal antibody	Interfering RNA
Patient Population	High Risk ASCVD	Recent ACS	High Risk ASCVD	Hyperlipidemia
Endpoint	CV events	CV events	CV events (Spire 2)	Lipid effects

OUTCOMES trial, a randomized investigation of alirocumab therapy, against a background of standard lipid-lowering therapy, in reducing major cardiovascular events. Approximately 18,000 patients 4-16 weeks post-acute coronary syndromes have been enrolled, and results are anticipated by early 2018.[15]

A third PCSK9 inhibitor, bococizumab, was well into clinical development until its clinical trial program was halted in November 2016 after neutralizing antidrug antibodies developed in a large number of patients, significantly diminishing the LDL lowering effects.[16] Unlike the other two available monoclonal antibodies to PCSK9, this agent is not fully "human" but instead "humanized", likely explaining the greater propensity for antibody formation. No neutralizing antibodies developed with evolocumab therapy in the FOURIER trial.[5]

Another mechanism of action of PCSK9 inhibition is in early clinical development. Inclisiran, a small "interfering RNA" which targets PCSK9 mRNA, has been shown in a phase II trial to produce sustained reductions in PCSK9 and LDL-C levels for up to six months, with a single subcutaneous injection, with greater efficacy demonstrated if a second injection is administered after 90 days.[17] Further investigations are moving forward in the ORION clinical trial program.

So where does PCSk9 inhibition fit in? The answer remains unclear. Currently the agents are labeled for use in patients with familial hypercholesterolemia with LDL-C>190 mg/dl, or in individuals with clinical atherosclerotic cardiovascular disease who require greater reduction in LDL cholesterol beyond that achieved on normally tolerated lipid lowering therapy. At what level of on-treatment LDL PCSK9 is indicated is undefined, and recent and ongoing studies appear to be inching that number downward. In FOURIER, the on-treatment LDL-C before PCSK9 inhibition was 92 mg/dl, and adding evolocumab significantly reduced events. Similar lipid levels are likely to be seen in ODYSSEY OUTCOMES. Stay tuned…

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