PCSK9 Inhibitors for LDL Lowering

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In 2003, families were described with a rare, autosomal dominant form of familial hypercholesterolemia due to gain of function mutations in proprotein convertase subtilisin/kexin type 9 (PCSK9) (1). Subsequent studies demonstrated that PCSK9 is secreted from liver and accelerates degradation of LDL receptors (2,3). Heterozygosity for PCSK9 null mutations in 2.6% of African-Americans was found to be associated with 28% reduction in LDL cholesterol (LDL-C) and an 88% reduction in CAD risk (4). These findings stimulated intense interest in PCSK9 as a pharmaceutical target. In this issue of Trends in Cardiovascular Medicine, Desai and Sabatine thoroughly review recent and ongoing trials of three monoclonal antibodies that disrupt PSCK9 binding to LDL receptors, leading to marked reductions in LDL-C (5). As detailed in their review, evolocumab (AMG145), alirocumab (SAR236553/REGN727), and bococizumab (RN316) given every 2-4 weeks, reduced LDL-C up to 75% in patients on statin therapy as compared to statin therapy alone, up to 51% in statin intolerant patients and other patients not in statin therapy, and up to 55% in patients with heterozygous familial hypercholesterolemia, most of whom were on statin therapy. Evolocumab reduced LDL-C up to 31% in patients with homozygous familial hypercholesterolemia, although there was no effect in LDL receptor-negative patients. Ongoing cardiovascular outcome trials that will rigorously test the ability of these agents to reduce major adverse cardiovascular events in high risk patients are also described.

PCSK9 is secretory serine endoprotease (6). Pro-PCSK9 is autocatalytically cleaved during its maturation in the golgi, but the prodomain remains tightly bound after secretion, precluding further catalytic activity (6). Effects of PCSK9 on LDL-C clearance thus do not depend on its protease activity. Rather, circulating PCSK9 binds the first epidermal growth factor-like repeat domain in the extracellular portion of the LDL receptor (6). Endocytosed LDL receptor is normally recycled back to the plasma membrane, but PCSK9 locks the receptor in an open conformation that targets it to lysosomes for degradation (6). The PCSK9-binding monoclonal antibodies under development disrupt this interaction and prevent LDL receptor degradation. Up to 40% of circulating PCSK9 is bound to LDL particles via a specific interaction
with apoB100 (6,7). Only free, unbound PCKS9 down regulates LDL receptors (6). PCSK9 does not bind VLDL or chylomicrons, suggesting that the interaction site may be unmasked during the intravascular remodeling of apoB100-containing lipoproteins (6,7). There is also a separate, intracellular pathway in which nascent PCSK9 binds LDL receptors and directs them from trans-golgi to lysosomes (8). However the extracellular pathway is the predominant mechanism of PCSK9-mediated LDL receptor degradation in vivo. Statins deplete intracellular cholesterol and upregulate LDL receptor transcription through sterol regulatory element-binding protein-2 (SREBP-2) (9). As PCSK9 transcription is also regulated by SREBP-2, PCSK9 levels are increased with statin therapy, which attenuates statins’ LDL-C lowering effects (9). Consistent with this, PCSK9 knockout mice exhibit an exaggerated LDL-C response to statin treatment (10).

Beyond its role in reducing LDL receptor levels, little is known about the biology of PCSK9. Its expression is highest in liver, and lower in kidney, intestine, brain, and lung (11). Evolocumab lowers lipoprotein(a) up to 30%, an effect also seen with other PCSK9 inhibitors (5). Statins do not decrease lipoprotein(a) and the LDL receptor is not thought to be involved in lipoprotein(a) clearance (12). So the mechanism of lipoprotein(a) lowering is not clear. PCSK9 inhibitors cause modest decreases in triglycerides (13). Some of this may reflect LDL receptor-dependent clearance of apoB containing remnant particles. However, decreased production of triglyceride-rich lipoproteins and upregulation of VLDL receptors may also contribute to the triglyceride lowering (7,14). VLDL receptor expression is increased in visceral adipose tissue of PCSK9 null mice, leading to an 80% increase in visceral adiposity (15). Intracellular degradation of apolipoprotein receptor 2 (ApoER2) is increased by PCSK9 (14). There is evidence that PCSK9 regulation of ApoER2 modulates neuronal apoptosis (16). PCSK9 has been shown to mediate degradation of LDL receptor-related protein-1 (LRP1) (14). LRP1 is widely expressed and has been implicated in inflammation and atherosclerosis. Other potential PCSK9 targets include the endothelial sodium channel (ENaC) and the hepatic receptor for hepatitis C virus, CD81 (7,14). The decrease in
Lipoprotein(a) with PCSK9 inhibitors may contribute to improved cardiovascular outcomes. However the implications of most of these observations for PCSK9 inhibitor therapy are unknown. Published trials of PCSK9 inhibitors have generally found adverse events, other than minor injection site reactions, to be comparable between groups (5). Moreover, the description of a few individuals in apparent normal health with undetectable circulating PCSK9 due to PCSK9 null mutations and LCL-C levels as low as 14 mg/dL offers some reassurance that PCSK9 inhibitors will not have serious on-target side effects (17). Ongoing long term trials of PCSK9 inhibitors and additional basic research on PCSK9 biology will provide important information on long term safety.

A specific concern with antibody-based therapies is immune reactions. These are much less likely with humanized and fully human antibodies, but can still occur (18). Most common are development of anti-drug antibodies, which in some cases can be associated with loss of therapeutic efficacy. For example, 28% of rheumatoid arthritis patients treated with adalimumab, a fully human antibody targeting tumor necrosis factor, developed anti-adalimumab antibodies over a three year period and these antibodies were associated with lower drug levels and decreased of therapeutic efficacy (19). Anti-evolocumab antibodies developed in 2/901 patients in one 52 week trial (13). In neither of these patients were the antibodies associated with loss of efficacy. More serious immune reactions can also occur. One patient on alirocumab developed leukocytoclastic vasculitis that responded to steroids and drug discontinuation (18). Large, current trials of PCSK9 inhibitors should clarify the extent to which immune reactions are a concern.

A recent post-hoc analysis of patients treated with alirocumab for a mean of 65 weeks found a 54% reduction of treatment emergent cardiovascular events (20). If ongoing trials demonstrate improved cardiovascular outcomes and good safety, as seems likely, patients with familial hypercholesterolemia and other LDL hyperlipidemias inadequately responsive to maximal statin therapy will be strong
candidates for addition of anti-PCSK9 therapy. As PCSK9 inhibitors have shown favorable tolerability versus ezitimibe in statin-intolerant patients, this group may also benefit (21). As noted by Desai and Sabatine, it is also possible that lowering LCL-C with PCSK9 inhibitors to levels below those recommended in current guidelines may offer additional benefit to very high risk patients (5). However this will need to be demonstrated in clinical trials. A trial of PCSK9 inhibitors in patients with advanced renal disease, a population in which the benefits of statins are unclear, would also be worthwhile (22). Overall, monoclonal antibodies targeting PCSK9 are a promising new therapy for LDL hyperlipidemia, and results of ongoing cardiovascular outcome trials are eagerly awaited.
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