A New Approach to Hypercholesterolemia

A quantum leap in managing difficult hypercholesterolemia may be close at hand. Unfortunately, hypercholesterolemia and high cardiovascular (CV) risk have become universal problems throughout the world. Al-Waili et al. in their case report on a mutation in the proprotein convertase subtilisin kexin type 9 serine protease (PCSK9) gene in Omani Arab patients with autosomal dominant familial hypercholesterolemia (ADFH), offered the first description of such a mutation in an Arab population and added emphasis to the possible importance of a new therapeutic approach that appears to be on the horizon.1

The Lipid Hypothesis

The lipid hypothesis that there is benefit from low density lipoprotein cholesterol (LDL-C) reduction was well established in the mid-1980s with publication of results from the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-PPT).2,3 Multiple other studies have shown the benefit of LDL-C reduction. Such studies include the Cholesterol Lowering Atherosclerosis Study (CLAS) using colestipol plus nicotinic acid with coronary artery plaque regression demonstrated by quantitative coronary angiography.4,5 Ileal bypass has been shown to result in significant LDL-C lowering in the Program on the Surgical Control of the Hyperlipidemias (POSCH) study. Percent lowering of LDL was 37.7% and five-year mortality including coronary heart disease (CHD) mortality, and/or nonfatal myocardial infarction was decreased significantly.6,7 Hypobetalipoproteinemia is a specific familial condition defined by LDL-C cholesterol equal to or less than the fifth percentile.8 Epidemiologic studies have shown that despite having some other associated medical problems, these individuals have a lower-than-average risk for CV disease.8 LRC-PPT, POSCH, and hypobetalipoproteinemia appear to be pure plays in showing the benefit of decreased LDL-C with no associated significant metabolic or pleiotropic effects. This also essentially appears to be the case with CLAS since the nicotinic acid used most likely added little additional benefit (over and above its further contribution to colestipol in decreasing LDL-C).

The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE-IT-TIMI 22) study looked at subgroups of LDL-C <40 mg/dL and LDL-C 40-60 mg/dL, in acute coronary syndrome patients. These subgroups were in comparison to higher LDL-C levels present in the rest of the PROVE-IT-TIMI 22 study and it was established that there were fewer major cardiac events in the lower LDL-C groups; this favorable decrease was statistically significant.8 It was concluded that as compared with PROVE-IT-TIMI 22 patients treated to an accepted LDL-C goal of 80-100 mg/dL, the lower LDL-C levels achieved resulted in improved clinical benefit with no adverse effects. A similar result was obtained in a subgroup of the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study of subjects attaining an LDL-C of <50 mg/dL.10 These subjects were found to have significantly fewer CV events as compared to the complete JUPITER study group.

In addition to currently being the single most effective class of medications to lower LDL-C, statins offer additional CV risk reduction from their multiple, pleiotropic effects.11 These pleiotropic effects include improved endothelial dysfunction, increased nitric oxide, antioxidant properties, decreased inflammation, and atherosclerotic plaque stabilization. Several classic outcomes studies have established CV risk reduction by LDL-C reduction using statins.12-15 These outcome studies offer further proof to the value of percent lowering of LDL-C, enhanced by the pleiotropic effects of the statin class of medications.

Therefore, the studies of LDL-C lowering that have been cited—with or without statins and their pleiotropic effects—strongly support the importance of targeting LDL-C. For the patient with an established high CV risk, such as the presence of diabetes mellitus, Grundy et al. defined the attainment of an LDL-C level of 70 mg/dL as desirable.16 In those high CV-risk patients with an LDL-C level already close to 70 mg/dL, the available evidence supports an even further percent reduction to well below this level. Lowering LDL-C still appears to be the gold standard for CV disease prevention.

Function of Normal PCSK9 and its Mutations

In 2007, in contrast to previous observations that mutations which increase activity of the protease PCSK9 are associated with increased LDL-C, Horton et al. reported that mutations that inactivate PCSK9 are associated with reduced LDL-C levels.17 This observation initiated thinking that inactivation of PCSK9 might be a new therapeutic target for LDL-C reduction and further prevention of CHD and CV disease.
The normal function of PCSK9 is to decrease LDL-C receptor levels by binding to these LDL-C receptors. This results in increased LDL-C. The function of these receptors is to initiate attachment of LDL-C to cells as the first step in LDL-C metabolism. Background information indicates that some mutations of PCSK9 can result in ADFH. On the other hand, other mutations can be associated with decreased LDL-C and an associated reduction in CV disease. The apparent mechanism is that some PCSK9 mutations with increased PCSK9 function decrease LDL-C receptor levels in the liver with a resultant increase in plasma LDL-C. In contrast, other mutations decrease PCSK9 function, leading to increased LDL-C receptors and a consequent reduction in plasma LDL-C.

Clinical Trials of Monoclonal Antibody to PCSK9

McKenney et al. evaluated the efficacy of a monoclonal antibody that binds to PCSK9. With the receptors bound by PCSK9, an increase in LDL-C results since it is metabolized less. This monoclonal antibody to PCSK9 is known as 5 SAR236553/REGN727 (SAR236553) and it is highly specific. In studies of patients with hypercholesterolemia, SAR236553 was shown to decrease LDL-C on a dose-dependent basis. This binding inhibits PCSK9 activity and thereby results in a favorable increase in LDL-C receptors with subsequent plasma LDL-C reduction. In the study by McKenney et al., the ability of SAR236553 to lower LDL-C at starting levels of LDL-C ≥100 mg/dL while taking stable atorvastatin therapy was tested. Stable therapy was defined as atorvastatin 10, 20, or 50 mg/ezetimibe, and in 1 patient given only placebo/ezetimibe. The reductions were all significant at p<0.001. Lipoprotein (a) was also decreased significantly. Myalgia measured by least squares mean was 43% and 55% respectively as compared to placebo (p<0.001 for both dose groups). This clinical trial with AMG 145 as a different monoclonal antibody to PCSK9 demonstrated marked LDL-C reduction. There were two serious adverse events not considered treatment-related.

In another trial (phase 2) with AMG 145, Sullivan et al. reported on the Goal Achievement after Utilizing and anti-PCSK9 antibody in Statin Intolerant Subjects (GAUSS) trial with intolerance to one or more statins because of muscle-related events. They administered AMG 145 or placebo subcutaneously every 4 weeks and the baseline LDL-C was on average, greater than 190 mg/dL. A total of 160 patients were randomized equally to 1 of 5 groups: AMG 145 alone at doses of 280 mg, 350 mg, and 420 mg; AMG 145 at 420 mg plus ezetimibe 10 mg/d, and placebo plus ezetimibe 10 mg/d. At week 12, LDL-C was decreased -51% (95% CI: -59% to -43%) in the 420 mg group, -63% (95% CI: 071% to -55%) in the 420 mg/ezetimibe group, and -15% (95% CI: -23% to -7.0%) in the placebo/ezetimibe group. The reductions were all significant at p<0.001. Lipoprotein (a) was also decreased significantly. Myalgia was the most commonly observed adverse event in one patient at 280 mg, 1 patient at 350 mg, 1 patient at 420 mg, 6 patients at 420 mg/ezetimibe, and in 1 patient given only placebo/ezetimibe.

Future Significance of PCSK9

Consideration of: 1. the lipid hypothesis that cholesterol lowering decreases CHD and CV disease, 2. that LDL-C is the gold standard for CHD and CV disease prevention, and 3. the current failure of lipid management to eliminate CHD and CV disease, all three emphasize the possible importance of new medications and approaches. An example of this failure of aggressive LDL-C reduction is that CV events in the major statin outcomes trials never attain even a 40% reduction status such as in the Scandinavian Simvastatin Survival Study (4S), where for example, myocardial revascularization procedures were only reduced 37% (p<0.00001). The statistics of this 4S study are impressive but the CHD and CV risk reduction are a long way from 100%. This isolated example demonstrates the need for additional therapeutic approaches. Without question, the monoclonal antibodies to PCSK9, SAR236553 and AMG 145, will effectively reduce LDL-C by percentages currently not attainable. The exception to this would be ADFH so severe that no normal LDL receptors were
available to be increased by the binding of PCSK9.25 Much needs to be learned by further clinical experience regarding any secondary effects. However, the evidence available supports the value of this marked LDL-C reduction unless some undocumented, secondary effects complicate the therapeutic approach of binding PCSK9 to attain significant LDL-C reduction. Such studies offer an exciting glimpse of a future frontier in decreasing CHD and CV disease risk, while getting closer to the apparent next frontier in the field, which is increasing HDL-C by the cholesterol ester transferase protein (CETP) inhibitor, anacetrapib, currently being evaluated in clinical trials.26 Although statins and their outcomes studies have changed the practice of CV medicine and offer patients much benefit, much remains to be done to prevent CV events. New medication classes such as the one SAR236553 and AMG 145 belong to will, of course bring some new problems for the patient and clinician (such as cost) and a more inconvenient necessary subcutaneous injection rather than as a daily oral medication. Nevertheless, the potential of SAR236553 and AMG 145 to block PCSK9 is exciting and offers an additional, promising approach to possibly improve the lives of patients at risk of/or already affected by atherosclerotic disease.

Conclusions

For CHD and other CV disease prevention, where maximum therapy still has less-than-desired benefit, the development of monoclonal antibodies to PCSK9 has created much interest. Increasing HDL-C may be closer as the next frontier in CHD and CV disease prevention but monoclonal PCSK9 antibodies have created much excitement and have even been heralded as the next statin-equivalent breakthrough.27 Decreasing LDL-C has good evidence to support it as the overall gold standard of CV disease prevention. If unforeseen problems do not plague the use of monoclonal PCSK9 antibodies, they may be a major frontier for CHD and CV disease management and prevention, especially for the many statin-intolerant patients, but even for the patient on a statin not at a target LDL-C level or a patient continuing to suffer CV events despite LDL-C levels normally considered ideal.

Availability of such PCSK9 antibody therapy could make a major difference for Omani ADFH patients and many other ADFH patients as described in the article of Al-Waili et al.1

References


