MEDNET
MEDICAL EDUCATION NETWORK

PRIORITY PRESS

Canadian Cardiovascular Congress (CCC)

Vancouver, BC / October 25-28, 2014

The LDL-C Treatment Gap Expected to Be Essentially Closed with New Lipid-Lowering Agents

Vancouver - Lipid-lowering therapies now in late stages of development are expected to bring the majority of patients to guideline-recommended treatment goals regardless of the reason why they are unable to reach their goal on current therapies. These new treatments have the potential to produce a second wave of reductions in morbidity and mortality commensurate with the one achieved after the introduction of statins. Of the lipid-lowering therapies in development, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are the most advanced. In the largest of the phase 3 trials yet conducted with a PCSK9 inhibitor, alirocumab achieved a LDL-C reduction of 61%. Outcome studies with this and other PCSK9 inhibitors are underway. In an early post-hoc analysis of the phase 3 study with alirocumab, cardiovascular (CV) risk reductions were consistent with those previously associated with large LDL-C reductions in statin trials.

Chief Medical Editor: Dr. Léna Coïc, Montréal, Quebec

In Canada, a substantial proportion of patients at risk for CV disease are not reaching the 2012 Canadian Cardiovascular Society (CCS) guideline-recommended goals for LDL-C on available lipid-lowering therapies. Although current data suggest most high-risk patients are now taking statins, goals continue to be missed for a number of reasons, including inadequate LDL-C reductions at doses of statins that are acceptably tolerated. This care gap is leaving a substantial proportion of patients vulnerable to preventable events.

In one ongoing international registry of patients with stable coronary artery disease (CAD) that includes 1200 Canadians, "the use of statin therapy [has now] crept up to 94%," reported Dr. Shaun Goodman, Associate Head, Cardiology, St. Michael's Hospital, Toronto. Yet, only 60% of patients in this registry, called CLARIFY, were at the CCS LDL-C goal of ≤2 mmol/L or a ≥50% reduction from baseline (Gandhi *et al. Can J Cardiol* 2012;28(5S): S224-S390).

Care Gap Hovers Near 40%

Published data suggest 35% to 40% of high-risk patients are not at their LDL-C goal, according to Dr. Goodman, citing several additional sets of data (Goodman *et al. Can J Cardiol* 2010;26;e33-35; Leiter *et al. Can J Diabetes* 2013;37:82-9). In many cases, this gap is due to the failure of the prescribing physician to employ adequate doses of high-intensity statins. Side effects, particularly muscle pain or weakness, also limit statin doses. For others, statins at maximum doses simply do not provide a sufficient lipid-lowering effect.

This care gap has been the focus of new therapies in development, particularly PCSK9 inhibitors. These agents are monoclonal antibodies that have reached phase 3 trials. Identified in Canada by Dr. Nabil G. Seidah, a researcher of the Institut de Recherches Cliniques de Montréal (IRCM), PCSK9 is a protein that binds to the LDL receptor (LDL-R) to induce its degradation. PCSK9 inhibitors preserve LDL-R to lower LDL-C serum concentrations. High degrees of efficacy and safety have been achieved in the phase 3 trials.

"Hopefully within a year or two, these drugs may be commercially available," reported Dr. Lawrence A. Leiter, Professor of Medicine and Nutritional Sciences, University of Toronto, Ontario. In a review of the current status of the three PCSK9 inhibitors that have reached clinical testing, Dr. Leiter provided data on phase 3 trials completed with alirocumab and evolocumab along with phase 2 data with bococizumab, which is at the least advanced stage of development.

Data from PCSK9 Inhibitor Trials

In his summary, Dr. Leiter reviewed several sets of data that were presented recently at the 2014 annual meeting of the European Society of Cardiology (ESC) from the alirocumab trials program, which is called ODYSSEY.

The largest, called ODYSSEY Long Term, evaluated efficacy and safety in 2,341 patients. Patients at high risk for CV events or who had heterozygous familial hypercholesterolemia (HeFH) were eligible. All were on maximum-tolerated doses of statins. They were randomized to 150 mg of alirocumab or placebo, both administered subcutaneously every 2 weeks. After 24 weeks the LDL-C change from baseline was a 61% reduction on alirocumab and a 0.8% increase on placebo, a relative 61.8% advantage (P<0.0001) for alirocumab. The treatment goals for very high-risk patients (<1.8 mmol/L) and high-risk patients (<2.6 mmol/L) were achieved in 81% of patients randomized to alirocumab versus 9% of those randomized to placebo (P<0.0001). Overall, 79% of alirocumab patients and 8% of placebo patients (P<0.0001) achieved an LDL-C <1.8 mmol/L regardless of risk. Patients on alirocumab, unlike patients on placebo, also had significant reductions from baseline in non-HDL-C, ApoB, and Lp(a).

These large improvements in dyslipidemia were achieved with a safety and tolerability profile that was "generally comparable" between the PCSK9 inhibitor and placebo groups, according to Dr. Leiter. In data he presented, the rate of treatment-emergent serious adverse events was in fact lower in the alirocumab than in the placebo group (16.5% vs. 17.6%), although the difference was not significant.

Ongoing, but not yet reported, the ODYSSEY Outcomes trial is designed to determine whether these large LDL-C reductions translate into a reduced risk of CV events. A post-hoc analysis

from the ODYSSEY Long Term trial reported by Dr. Leiter was encouraging. Using the same primary endpoint as the ODYSSEY Outcomes (death due to coronary heart disease, non-fatal myocardial infarction, fatal and non-fatal ischemic stroke, and unstable angina requiring hospitalization), the rates were 1.4% in the alirocumab arm versus 3.0% in the placebo arm. While cautioning about the limitations of a post-hoc observation, Dr. Leiter noted this is "about a 50% lower event rate" that is "very reassuring in regard to cardiovascular safety."

LDL-C reductions have also been encouraging with evolocumab and bococizumab. In the phase 3 DESCARTES study, evolocumab was associated with a 57% reduction in LDL-C relative to placebo ($P<0.001$) at week 52. In a 12-week, phase 2b safety and dose-ranging study, bococizumab achieved a comparable LDL-C reduction on the highest dose. Rates of adverse events have been low in studies with evolocumab and bococizumab. Bococizumab, unlike alirocumab and evolocumab, is a humanized rather than a fully human monoclonal antibody.

First PCSK9 Agent with 76-Week Data

An international open-label extension trial with alirocumab in HeFH patients now has data available out to 76 weeks. All patients in the study were on stable doses of a statin. Ezetimibe was permitted. In the most recent update of the study, which included Canadian participants and was presented at the CCC, the average reduction in LDL-C from baseline was 60.5% ($P<0.0001$), reported Dr. Robert Dufour, Associate Director, Clinic for Cardiovascular Risk Prevention, IRCM, Montreal. Alirocumab has been well tolerated and associated with good long-term compliance, with more than 90% of patients remaining on alirocumab in a dose of 150 mg administered every 2 weeks. No patient discontinued treatment due to an injection-site reaction.

LDL-C Reduced in Familial Disease

Impressive reductions were also achieved in two similarly designed trials that enrolled patients with HeFH. In the pooled analysis of 735 patients, the LDL-C reductions for alirocumab relative to placebo exceeded 51% at 24 weeks ($P<0.0001$) and were sustained at 52 weeks. A placebo-like safety profile was again observed in this study with a lower but not statistically different rate of discontinuation for side effects in the alirocumab relative to the placebo arm (3.1% vs. 3.7%).

The long-term efficacy of alirocumab for HeFH is encouraging, but PCSK9 inhibitors are not the only new strategy being pursued for groups not reaching treatment goals. The need for novel strategies is particularly acute in patients with forms of homozygous familial hypercholesterolemia (HoFH), and several lines of research in this area are being pursued, according to Dr. Jacques Genest, Professor of Medicine, McGill University Health Center, Montreal. In fact, Dr. Genest reported that one new agent for HoFH, lomitapide, has already been approved in Canada, and another, mipomersen, is in development. Extracorporeal LDL filtration machines have also been used experimentally to reduce LDL-C.

LDL-C: Evidence of Benefit from Very Low Levels

Even when very low LDL-C levels are achieved, there is still no evidence of an increased risk of adverse events, emphasized Dr. Genest. Rather, in analyses of patients who achieved very low LDL-C levels (<1.0 mmol/L) in trials such as JUPITER, PROVE-IT, and TNT, "there has been a very strong trend" towards reduced events relative to those with higher levels, Dr. Genest reported. At the same time, Dr. Genest observed that there has been "no increase in adverse events," even in detailed evaluations of specific types of events for which there is theoretical concern, such as neurological dysfunction.

Dr. G. B. John Mancini, Professor of Medicine, University of British Columbia, Vancouver, provided similar reassurance. According to Dr. Mancini, who traced a linear relationship between elevated LDL-C and increased CV risk across a broad range of evidence, there is abundant evidence to support the current Canadian guidelines and a potential for even lower LDL-C goals to provide additional risk reduction. In agreement with Dr. Genest, he concluded on the basis of his evaluation that "side effect profiles at very low levels of LDL-C do not yet show worrisome trends that would negate the CV benefits."

Conclusion

A substantial proportion of patients currently receiving statins are not at guideline-recommended goals for LDL-C. The reasons for this care gap are likely to include both failure to prescribe high-intensity statins in sufficiently rigorous regimens and the inability of statins to reach goals at acceptably tolerated doses. Most of these patients, including those with HeFH, have achieved guideline goals on PCSK9 inhibitors in large clinical trials. Preliminary evidence with alirocumab has linked these additional LDL-C reductions with lower rates of CV events. More information on the clinical role of PCSK9 inhibitors, which appear to have an excellent safety and tolerability profile, is expected from ongoing studies. □

Note: At press time, PCSK9 inhibitors are not available in Canada.

To view an electronic version of this publication along with related slides if available, please visit mednet.ca/go/?pn=pp15-010e

Medical Education Network Canada Inc. 132 chemin de l'Anse, Vaudreuil, Quebec J7V 8P3

PP15-010E RM