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Lessons from the trials

OSLER and ODYSSEY LONG TERM: PCSK9 inhibitors on the right track of reducing cardiovascular events

Mohamed Hassan*

Division of Cardiology, Aswan Heart Centre, Aswan, Egypt
*Email: mohamed.daoud@yahoo.com

ABSTRACT

Proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors have emerged as a novel treatment option in patients with hypercholesterolemia. Evolocumab and alirocumab have achieved consistent and significant (around 60%) reduction in low-density lipoprotein cholesterol (LDL-C) levels when added to statin therapy in short term studies. The Open-Label Study of Long-term Evaluation Against LDL-C (OSLER), and The Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM) studies are two phase 3, multicentre, randomized, placebo controlled studies that were conducted to evaluate the long term efficacy and safety of evolocumab and alirocumab respectively in reducing lipids and cardiovascular (CV) events. Both studies demonstrated additional 48–53% reduction of CV events when added to statin therapy. Most adverse events occurred with similar frequency in the two groups; however the rate of neurocognitive adverse events was higher with evolocumab and alirocumab than with placebo. These data provide strong support for the notion that lower LDL-C goal is better, and may confirm the role of PCSK9 inhibitors as a new frontier in lipid management. The results of larger long-term outcome studies are still awaited.

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INTRODUCTION

Evolocumab and alirocumab are monoclonal antibodies that bind to proprotein convertase subtilisin kexin 9 (PCSK9) and inhibit its interaction with LDL receptors. PCSK9 inhibitors have emerged as a novel treatment option in patients with hypercholesterolemia.[1,2]

The addition of evolocumab[3–7] or alirocumab[8–10] to background statin therapy has achieved significant and sustained reduction in low-density lipoprotein cholesterol (LDL-C) levels in patients with varying levels of cardiovascular (CV) risk. However, the long-term effects of these drugs on the clinical outcome have not been yet confirmed.

Data about the long term efficacy and safety of evolocumab and alirocumab in reducing CV events have been recently released and reviewed here.

OSLER-1 AND -2 STUDIES

The Open-Label Study of Long-term Evaluation Against LDL-C (OSLER)-1 and -2 studies were open label, multicentre, randomized, controlled studies that were designed to assess the long-term efficacy and safety of evolocumab in reducing lipids and CV events. Data from the OSLER-1 and OSLER-2 trials were combined into a single analysis set and were recently presented at the American College of Cardiology (ACC) 2015 Scientific Sessions and simultaneously published in the *New England Journal of Medicine* in March 2015.[11] The OSLER-1 study recruited patients who had completed one of the five phase 2 parent studies of evolocumab at 190 centers, while the OSLER-2 trial was conducted at 305 centers that participated in at least one of the seven phase 3 studies of evolocumab.

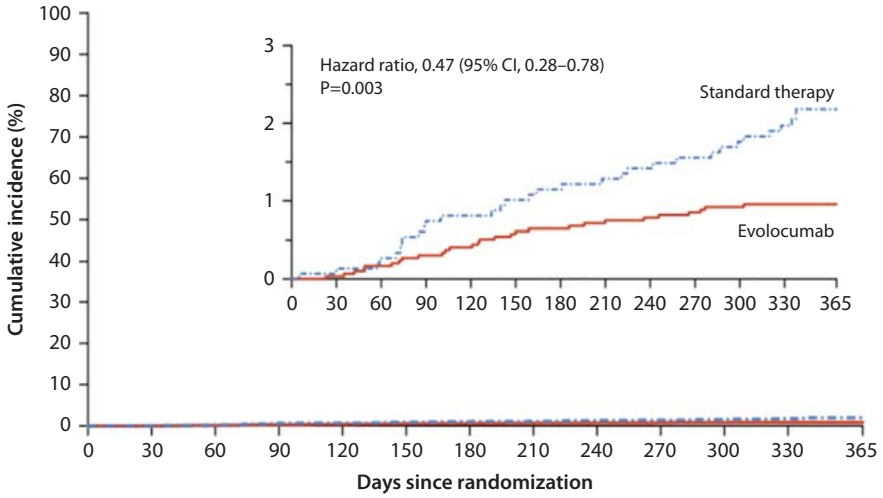
Regardless of the assignment in the parent study, a total of 4465 eligible patients (1324 patients in OSLER-1, and 3141 patients in OSLER-2; representing 74.1% of eligible patients in all parent studies) were randomly assigned in a 2:1 ratio to receive either subcutaneous (SC) evolocumab 140 mg every 2 weeks or 420 mg monthly in addition to their standard therapy or standard therapy alone. The primary end-point in the two trials (as a pre-specified exploratory analysis) was the incidence of adverse CV events including death, myocardial infarction (MI), unstable angina, coronary revascularization, stroke, transient ischemic attack, and heart failure. The secondary end-points were the percent change from baseline in the LDL-C level, and other lipoproteins. Safety end-points included serious adverse events, adverse events leading to the discontinuation of the study drug, creatine kinase and hepatic enzyme elevations, and the development of anti-evolocumab antibodies.

After a median follow up period of 11.1 months, evolocumab achieved 61% reduction of LDL-C level (95% confidence interval [CI] $= 59$ to 63; $P < 0.001$) as compared to standard therapy. Evolocumab reduced levels of non-HDL cholesterol by 52%, apolipoprotein B by 47.3%, triglycerides by 12.6%, and lipoprotein (a) by 25.5% ($P < 0.001$), and raised levels of HDL cholesterol (HDL-C) by 7.0%. Patients in the evolocumab group had a significantly lower rate of all CV events than the standard-therapy group (0.95% vs. 2.18% respectively; hazard ratio 0.47; 95% CI = 0.28 to 0.78; $P = 0.003$) (Figure 1, 2).

Most adverse events occurred with similar frequency in the two groups. The rate of neurocognitive adverse events was higher in the evolocumab group than in placebo group (0.9% vs. 0.3% respectively), however no relation was found to the LDL-C level during treatment. No binding or neutralizing antibodies to evolocumab were detected.

ODYSSEY LONG TERM STUDY

The Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM) study was a phase 3, multicentre, randomized, double- blind, placebo-controlled study that has been recently published in the New England Journal of Medicine in March 2014.12 A total of 2341 patients with heterozygous familial hypercholesterolemia, established coronary heart disease (CHD), or CHD risk equivalent (defined as peripheral arterial disease, ischemic stroke, chronic kidney disease, or diabetes mellitus plus two or more additional risk factors [hypertension; ankle–brachial index of ≤ 0.90; microalbuminuria, macroalbuminuria; preproliferative or proliferative retinopathy; or a family history of premature CHD]) were included in the study if they had an LDL-C level ≥ 70 mg/dL despite receiving maximum tolerated dose of statin therapy. Eligible patients were randomly assigned in a 2:1 ratio to receive SC alirocumab (150 mg) or placebo every 2 weeks for 78 weeks. The primary efficacy end-point was the percentage change from baseline in LDL-C level at week 24 (based on intention-to-treat analysis). Secondary end-points included the percentage change from baseline in LDL-C level



No. at Risk													
Standard therapy	1489	1486	1481	1473	1467	1463	1458	1454	1447	1438	1428	1361	407
Evolocumab	2976	2970	2962	2949	2938	2930	2920	2910	2901	2885	2871	2778	843

Figure 1. Cumulative incidence of cardiovascular events in OSLER studies (From Sabatine et al.[11]).

(based on per protocol analysis), as well as other lipoproteins at weeks 12 and 24 in both the intention-to-treat analysis and per protocol analysis. A post hoc analysis was performed to compare the rate of major CV events (the composite of death from CHD, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) between both study groups.

Patients assigned to alirocumab had 61% reduction in LDL-C level at week 24 compared to 0.8% increase in LDL-C in placebo group ($p < 0.001$) (Figure 2). This effect was consistent over the whole study period and reached 58% LDL-C reduction at 78 week in the per protocol analysis. The alirocumab group had significant greater reduction from baseline in serum triglycerides level (−17.3 percentage points) and modest increase in levels of HDL-C level (4.6 percentage points) as compared to placebo group. There was a significant reduction in levels of lipoprotein (a) in alirocumab group compared to placebo (−29.3% vs. −3.7% respectively, $p < 0.001$). The rate of major adverse CV events was significantly lower with alirocumab than with placebo (1.7% vs. 3.3% respectively; hazard ratio 0.52; 95%CI = 0.31 to 0.90; $p = 0.02$) (Figure 2). Patients received alirocumab had higher rates of myalgia

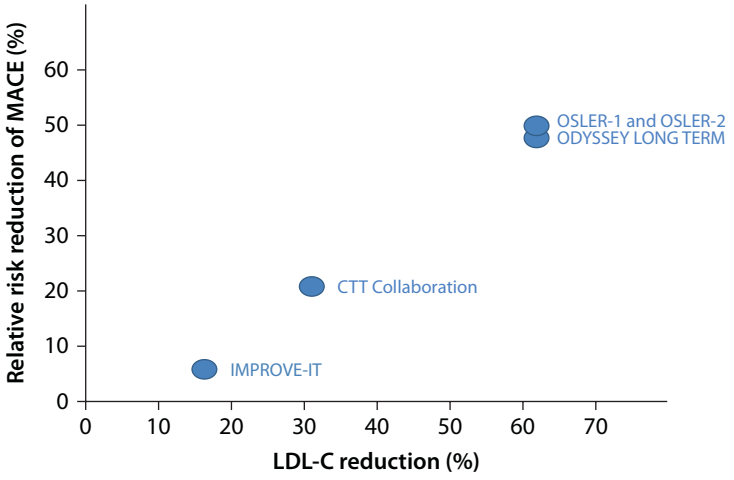


Figure 2. Relative risk reduction of major adverse CV events (MACE) with PCSK9 inhibitors (OSLER and ODYSSEY LONG TERM studies) compared to statins (CTT Collaboration database), and ezetimibe (IMPROVE-IT study). CTT, Cholesterol Treatment Trialists Collaboration; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial (From Gencer et al.[12]).

(5.4% vs. 2.9%, p = 0.006), neurocognitive events (1.2% vs. 0.5%, p = 0.17), and ophthalmologic events (2.9% vs. 1.9%, p = 0.65) compared to those received placebo.

DISCUSSION

In line with our prior expectations, PCSK inhibition gained further support for possible US Food and Drug Administration (FDA) approval especially in patients with statin intolerance or familial hypercholesterolemia in whom target LDL-C level could not be achieved by statin therapy. Consistent with the results of previous short-term trials, both evolocumab and alirocumab achieved about 60% reduction from baseline in LDL-C concentration in the longer-term studies. Even though the analysis was exploratory, combined data from OSLER-1 and 2 studies demonstrated also significant reduction of CV events by 53% at one year in patients who received evolocumab compared with standard statin therapy. Similarly, alirocumab yielded 48% lower CV events - when added to statins at maximum tolerated dose- than placebo in the ODYSSEY LONG TERM study.

Since the introduction of PCSK9 inhibitors, Impairment of neurocognitive function was a major concern with such drastic reduction in LDL-C level. Cholesterol is an important component of neurons, and PCSK9 is involved in cortical neuron regeneration.[13] However, lipoproteins and monoclonal antibodies do not cross the blood brain barrier. In addition, PCSK9 loss-of-function variants have not been associated with impaired cognitive performance.[14] Despite the low overall rate of neurocognitive adverse events (<1%) in OSLER and OSYSSEY LONG TERM studies, the rate of neurocognitive events was higher with evolcumab (0.9% vs. 0.3%), and with alirocumab (1.2% vs. 0.5%) than placebo. However, no correlation was detected between these events and the degree of LDL-C reduction.

While the findings are highly encouraging, these studies have several limitations:

- The study participants of the OLSER studies had already completed a previous study. Patients who could not tolerate the drug in the parent short-term studies were not included.
- Coronary revascularization was the most frequently reported CV event in the OSLER studies. There is some concern that the decision of revascularization and reporting adverse events could have been influenced by the open label design of the studies and knowing the treatment assignment.
- The number of patients is relatively small and the duration of follow-up is too short to be considered definitive. We are still waiting the results of the two ongoing large scale, more informative, and better designed studies; (1) FOURIER (Further Cardiovascular Outcomes Research with PCSK9 inhibition in Subjects with Elevated Risk) study which is the main study designed by Amgen to address the effect of evolocumab on adverse CV events in 22,500 patients and the results are expected to be released in 2017 (2). ODYSSEY OUTCOMES study which is the main study designed by Sanofi to provide an assessment of the CV benefit of alirocumab in 18,000 patients over a period of 5 years.
- The overall rate of CV events in both studies is relatively low (60 events in total (1.3 %) in OSLER studies, and 53 events (2.2%) in ODYSSEY study).
- Patients receiving evolocumab had more visits during follow up which might give them more opportunity to report more adverse events.
- Neurocognitive events were self-reported by patients. No formal neurocognitive testing was used in these studies. On the contrary, FOURIER study includes a substudy that will include formal neurocognitive testing using validated instruments.

WHAT HAVE WE LEARNED?

The data from PCSK9 trials, together with IMPROVE-IT results, provide strong support for the notion that lower LDL-C goal is better (Figure 2). PSCK inhibitors are going in the right track to be a new frontier in lipid management with the expectations of having a great role in decreasing the residual CV risk. However, the results of the larger long-term outcome studies are still awaited.

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