

New Clinical Trials With Evolocumab and Alirocumab on Cardiovascular Outcomes, in Patients With High Risk of Acute Coronary Syndromes

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ABSTRACT

Evolocumab, alirocumab and bococizumab are leading monoclonal antibodies that are called Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. These agents have been used in multicenter studies to demonstrate their efficacy and safety and effect on blood lipoproteins as well as on cardiovascular outcomes indicating significant beneficial effects without much adverse effects.

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Key words: Monoclonal antibody; PCSK9 inhibitors; Coronary syndrome; Coronary artery disease; Dyslipidemia

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INTRODUCTION

Evolocumab, alirocumab and bococizumab are monoclonal antibodies on which maximum research has been conducted humans. These agents are called Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which have been tried in multicenter studies to demonstrate their efficacy and safety and effect on blood lipoproteins^[1-4]. Recently evolocumab and alirocumab have been demonstrated to have beneficial effects on cardiovascular events which appears to be a new achievement in the treatment of coronary artery disease (CAD)^[1,2]. Randomized, controlled intervention trials with both the agents have demonstrated the efficacy and safety of these agents in reducing blood lipids without a decrease in HDL cholesterol^[1-4]. It is possible that treatment with PCSK9 inhibitors can cause further decline in acute coronary syndromes (ACS) among high risk patients receiving statins.

Following acute coronary syndrome (ACS), the risk for future cardiovascular events (CVEs) is high and is related to levels of low-density lipoprotein cholesterol (LDL-C) even within the setting of intensive statin treatment. PCSK9 regulates LDL receptor expression and circulating levels of LDL-Cholesterol, and monoclonal antibodies can produce substantial and sustained reductions of LDL-C. The ODYSSEY Outcomes trial tests the hypothesis that treatment with alirocumab, a fully human monoclonal antibody to PCSK9, improves cardiovascular outcomes after ACS^[5]. This trial will determine whether the addition of the PCSK9 antibody alirocumab to intensive statin therapy reduces cardiovascular diseases (CVDs) after ACS. This Phase 3 study will randomize approximately 18,000 patients to receive biweekly injections of alirocumab (75-150 mg) or matching placebo^[5].

MECHANISMS

Many enzymes, such as PCSK9, are inactive when they are first synthesized, because they have a section of peptide chains that blocks

their activity. Proprotein convertase enzyme removes that section to activate the enzyme^[6]. PCSK9 in humans is encoded by the PCSK9 gene and it binds to the epidermal growth factor-like repeat A (EGF-A) domain of the LDL receptor inducing LDLR degradation. Reduced LDLR levels result in decreased metabolism of LDL-C, which could lead to hypercholesterolemia. It is also possible that PCSK9, one of the serine proteases, increases LDL cholesterol because it binds to LDL receptors, leading to their accelerated degradation resulting in to increased LDL cholesterol levels^[3]. Thus PCSK9 inhibitors act by preventing degradation of LDL receptors resulting in to increased LDL receptor activity on hepatocytes close to physiological function. Further details about monoclonal antibodies in relation to statin therapy on blood lipids have been presented by other workers^[6].

PHASE 3 TRIALS ON CARDIOVASCULAR OUTCOMES

In phase 3 trials, evolocumab a fully human monoclonal antibody has demonstrated typically to achieve approximately a 60% reduction in LDL cholesterol levels when administered at the optimal doses^[3,4]. Among subjects ($n=72$; 40 intravenously and 32 subcutaneously) receiving REGN727, there were no discontinuations because of adverse events with significant reduction in LDL cholesterol levels in all the studies. Alirocumab is another monoclonal antibody that inhibits PCSK9 levels and has been demonstrated to decrease LDL cholesterol levels in patients who are receiving statin therapy^[2].

In both monoclonal antibody trials using evolocumab and alirocumab, the investigators assessed adjudicated cardiovascular events; death, myocardial infarction, unstable angina, coronary revascularization, stroke, transient ischemic attack, and heart failure, as a prespecified exploratory analysis^[1,2]. In the evolocumab trials, which included two open-label, randomized trials, the authors enrolled 4,465 patients, mean age 58 years, (1,324 patients in OSLER-1 and 3,141 patients in OSLER-2) who had completed 1 of 12 phase 2 or 3 studies^[1]. The eligible patients were randomly assigned in a 2:1 ratio to receive either evolocumab (140 mg every 2 weeks or 420 mg monthly) plus standard therapy or standard therapy alone. Of the 4,465 patients, 2,976 received evolocumab plus standard therapy and 1,489 received standard therapy alone for a median duration of follow-up of 11.1 months. Results of the combined data from the these trials revealed that evolocumab significantly reduced the concentration of LDL cholesterol by 61%, from a median of 120 mg per deciliter to 48 mg per deciliter compared with standard therapy alone ($P<0.001$). The rate of cardiovascular events at 1 year was reduced from 2.18% in the standard-therapy group to 0.95% in the evolocumab group (hazard ratio in the evolocumab group, 0.47; 95% confidence interval, 0.28 to 0.78; $p=0.003$).

The alirocumab trial, involved 2341 high risk patients with LDL cholesterol levels of 70 mg per deciliter (1.8 mmol per liter) or

more, and all patients were receiving treatment with statins at the maximum tolerated dose, with or without other hypolipidemic agent. All the subjects were randomly assigned in a 2:1 ratio to receive alirocumab (150 mg) or placebo as a 1-ml subcutaneous injection every 2 weeks for 78 weeks (2). After 24 weeks, the difference between the alirocumab and placebo groups in the mean percentage change from baseline in calculated LDL cholesterol level was -62% ($P<0.001$). After 78 weeks, the rate of major cardiovascular events (death from nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) was significantly lower with alirocumab than with placebo (1.7% vs. 3.3%; $p=0.02$). It is clear that treatment with alirocumab, when added to statin therapy at the maximum tolerated dose, can significantly reduce LDL cholesterol levels with a significant decline in the rate of cardiovascular events.

ADVERSE EFFECTS

The risk of adverse events, including neurocognitive events, did not vary significantly according to the achieved level of LDL cholesterol but neurocognitive events were slightly more frequent in the evolocumab group (1) (Table 1). Evolocumab was discontinued by 7.1% of the patients and a total of 3128 patients (70.1%) were receiving statin therapy at the start of the OSLER trials. The incidence of adverse events were observed in 2060 of 2976 patients (69.2%) in the evolocumab group and in 965 of 1489 patients (64.8%) in the standard-therapy group. Serious adverse events were also similar in the two groups; 222 (7.5%) vs 111 (7.5%) patients, in the evolocumab and standard-therapy group, respectively. Neurocognitive adverse events were <1%, but such events were unrelated to LDL cholesterol and more frequently observed in the evolocumab group. The incidence of new evolocumab-binding antibodies were nonsignificant; 9 patients (0.3%) in the evolocumab group and in 4 patients (0.3%) in the standard-therapy group. Reactions at injection site were reported in 129 (4.3%) subjects in the evolocumab group and in 6 (0.2%), drug was discontinued. In the alirocumab trial, there were higher rates of injection-site reactions (5.9% vs 4.2%), myalgia (5.4% vs 2.9%), neurocognitive events (1.2% vs 0.5%), and ophthalmologic events (2.9% vs 1.9%) in the experimental intervention group compared to control group. The findings indicate that evolocumab appears to better safety profile compared to alirocumab, however both the agents may be used for further decline in CVEs among high risk patients receiving statins.

It seems that the efficacy and safety of these agents has to be established in further larger and longer-term studies. Because, hospitalization for unstable angina and heart failure, coronary revascularization by angioplasty and transient ischemic attack, are considered soft end points which are open to bias in both the trials^[1,2]. Apart from developed countries, coronary risk factors and CAD have

Table 1 Adverse cardiovascular events during follow up in both trials number (%).

Event, n (%)	Alirocumab (n=1550)	Placebo (n=788)	Evolocumab (n=2976)	Placebo (n=1489)	Total drugs (n= 4526)	Placebo (n=2277)
Fatal and nonfatal stroke	9 (0.6)	2 (0.3)	4 (0.14)	7 (0.47)	13(0.287)	9(0.395)
Non-fatal MI	14 (0.9)*	18 (2.3)	22 (0.75)	18 (1.30)	36(0.795)	36(1.581)
Total Major CVE	27(1.74)*	27(3.42)	30(1.008)*	31(2.082)	57(1.259)*	58(2.547)
Total Cardiovascular events,	72 (4.6)	40 (5.1)	29 (0.95)*	31 (2.18)	101(2.231)*	71(3.118)
CHF requiring hospitalization	9 (0.6)	3 (0.4)	1 (0.03)	1 (0.07)	10(0.22)	4(0.17)
Unstable angina requiring hospitalization	0	1 (0.1)				
Ischemia driven coronary revascularization procedure	48 (3.1)	24 (3.0)				
Total deaths	4 (0.3)	7 (0.9)	4 (0.14)	6 (0.41)	8 (0.177)	13(0.570)

*=Total deaths= $p<0.035$ for alirocumab,0.073 for evolocumab, 0.0056 for combined; **= Total major cardiovascular end points= $p<0.0035$ for evolocumab,0.0001 for combined.

become a public health problem in emerging countries, hence these agents could be important for prevention of risk of CAD including acute coronary syndromes and in all countries^[5-12].

CONCLUSIONS

In brief, PCSK9 inhibitors can cause 50-60% reduction in LDL cholesterol levels, resulting in to significant decline in cardiovascular events without any significant adverse effects. Larger long term, double blind trials are necessary to confirm the safety and efficacy of these agents in the prevention of cardiovascular diseases. The FOURIER study (NCT01764633) which is a randomized, placebo controlled ongoing trial aims to provide a more accurate assessment of the cardiovascular benefit of evolocumab. The FOURIER study is involving 27,500 high-risk patients with CVD who are receiving background statin therapy. The primary end point is a composite of cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization. Other trials of alirocumab and bococizumab to evaluate cardiovascular outcomes are also in progress (NCT01663402, NCT01975376, and NCT01975389).

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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