for both Q2W and Q4W administration was demonstrated: 40%, 64%, and 72% with 50 mg, 100 mg, and 150 mg Q2W, respectively, and 43% and 48% with 200 and 300 mg Q4W. At Week 12, LDL-C reduction with placebo was 5.1% (Table 1). SAR236553 also increased the rate of achievement of LDL-C goals (<70 mg/dL) compared with placebo. Of note, LDL-C reductions were generally unaffected by the baseline atorvastatin dose.

Table 1. Changes in LDL-C from Baseline to Week 12 by Treatment Group (mITT Population).

Intervention	Baseline LDL-C (mg/dL)	Percent Change LDL-C[1]
Placebo	130.2	-5.1 (3.1)
SAR236553 50 mg Q2W	123.2	-39.6 (3.2)*
SAR236553 100 mg Q2W	127.0	-64.2 (3.1)*
SAR236553 150 mg Q2W	123.9	-72.4 (3.2)*
SAR236553 200 mg Q4W	128.2	-43.2 (3.3)*
SAR236553 300 mg Q4W	131.6	-47.7 (3.2)*

p<0.0001 for percent change SAR236553 versus placebo; [1]LS mean (SE), using LOCF method.

SAR236553 produced consistent and robust reductions in all other Apo B-containing lipoproteins (Table 2), with important decreases in lipoprotein(a)—a finding that is consistent with the prior Phase 1 studies [Stein EA et al. *N Engl J Med* 2012]. There was also a trend toward lower triglycerides and increases in high-density lipoprotein cholesterol (HDL-C) and Apo AI versus placebo—findings that were not entirely explained by the direct mechanism of action of PCSK9 inhibition. The biweekly injections appeared to deliver a more sustained LDL-C reduction over the Q4W dosing schedule.

Table 2. Changes in ApoB, Non-HDL-C, and Lp(a) from Baseline to Week 12 by Treatment Group (mITT Population).

Intervention	% Change Apo B	% change Non-HDL-C	% Change Lp(a)
Placebo	2.2	-2.2	0.0
SAR236553 50 mg Q2W	-27.3*	-33.6*	-13.3†
SAR236553 100 mg Q2W	-48.1*	-55.6*	-26.1*
SAR236553 150 mg Q2W	-56.1*	-62.5*	-28.6*
SAR236553 200 mg Q4W	-28.7*	-37.4*	-16.7†
SAR236553 300 mg Q4W	-33.1*	-40.7*	-7.9†

*p<0.0001 for percent change SAR236553 versus placebo; †p=0.05 for percent change SAR236553 versus placebo; p values are not adjusted for multiplicity (descriptive only).

SAR236553 was well tolerated during the study, with no signs of persistent or prevalent clinical or laboratory adverse events, including those that were associated with hepatic and muscle assessments. One patient who was assigned to the 300-mg Q4W regimen developed a rare complication, leukocytoclastic vasculitis, an inflammatory immune complex-mediated vasculitis of small-caliber blood vessels, although no similar reactions have been reported. No antidrug antibodies were observed 2 weeks before or after the incident.

According to Dr. McKenney, these results support further evaluation of this novel biologic lipid-lowering therapy in large, multicenter, randomized, controlled trials. Plans are underway to evaluate if PCSK9 antibody therapy can reduce adverse cardiovascular outcomes among an internationally diverse patient population who are taking a variety of different background lipid-lowering therapies.

Oral Rivaroxaban Alone for Symptomatic Pulmonary Embolism

Written by Maria Vinall

Rivaroxaban, a direct, specific, competitive factor Xa inhibitor that inhibits thrombin generation, is an effective treatment for venous thromboembolism (VTE). The Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep-Vein Thrombosis or Pulmonary Embolism trial [EINSTEIN PE; Buller HR et al. *N Engl J Med* 2012] reported data that showed that rivaroxaban was noninferior to standard therapy but had a superior bleeding profile in patients with pulmonary embolism (PE). Results were presented by Harry Roger Buller, MD, Academic Medical Center, Amsterdam, The Netherlands.

This was a multicenter, randomized, open-label, assessor-blind, event-driven, noninferiority trial that comprised patients with acute symptomatic PE with or without deep-vein thrombosis (DVT). Patients (n=4832) were randomized to receive open-label oral rivaroxaban 15 mg twice daily for 3 weeks, then 20 mg once daily, versus subcutaneous enoxaparin (1 mg/kg) twice daily for 5 days plus a vitamin K antagonist (VKA; acenocoumarol or warfarin), initiated within 48 hours of randomization. Enoxaparin was discontinued when the patient's international normalized ratio (INR) was ≥2.0 for 2 consecutive days after at least 5 days of enoxaparin treatment. INR was measured at least once a month and the dose of the VKA was adjusted to maintain an INR of 2.0 to 3.0. The study treatment duration was 3, 6, or 12 months, and patients were followed for 30 days post-treatment. The primary efficacy outcome was first

recurrent VTE (defined as fatal or nonfatal PE or DVT). The principal safety outcome was the first major or nonmajor clinically relevant bleeding.

In this population of patients with acute symptomatic PE with or without DVT, rivaroxaban was noninferior to enoxaparin, followed by VKA for efficacy (2.1% vs 1.8%; HR, 1.12; 95% CI, 0.75 to 1.68; p=0.003 for a noninferiority margin of 2.0). Significantly fewer patients who were randomized to rivaroxaban had major bleeding compared with those who were treated with enoxaparin/VKA (1.1% vs 2.2%; HR, 0.49; 95% CI, 0.31 to 0.79; p=0.003). Major or nonmajor clinically relevant bleeding occurred in 10.3% of the rivaroxaban- versus 11.4% of enoxaparin/VKA-treated patients (HR, 0.90; 95% CI, 0.76 to 1.07; p=0.23). Primary efficacy and safety outcomes were similar between the two treatments, irrespective of age, body weight, gender, kidney function, and cancer. There was no difference in liver toxicity.

The investigators concluded that oral rivaroxaban, 15 mg twice daily for 3 weeks, followed by 20 mg once daily, provides patients and clinicians with a simple, single-drug approach for the acute and continued treatment of both DVT and PE, with a potential improvement in the benefit/risk profile.

Neutral Outcomes But Important Insights From FOCUS-CCTRN

Written by Rita Buckley

Cell therapy has emerged as an exciting and innovative approach for treating patients with advanced ischemic heart disease, including those with refractory angina and/or heart failure [Perin EC et al. *JAMA* 2012]. The FOCUS-CCTRN trial [NCT00824005] was designed to evaluate the safety and efficacy of bone marrow mononuclear cells (BMCs) in patients with chronic ischemic heart disease and left ventricular (LV) dysfunction with no other revascularization options. Emerson Perin, MD, PhD, Texas Heart Institute, St. Luke's Episcopal Hospital, Houston, Texas, USA, presented data from the study, the largest to date on autologous bone marrow therapy in patients with chronic ischemic heart disease.

Prior smaller studies had suggested that BMCs would provide benefit for patients with ischemic cardiomyopathy. The primary objective of FOCUS-CCTRN was to determine if transendocardial administration of 100 X 10^6 total BMCs improved measures of LV performance and perfusion at 6 months compared with baseline levels. Coprimary endpoints included left ventricular end systolic volume (LVESV), maximal oxygen consumption (MVO_2), and change in ischemic (reversible) defect size.

The study enrolled symptomatic patients (NYHA classification III or Canadian Cardiovascular Society classification II–IV) with a LV ejection fraction (LVEF) ≤45% a perfusion defect by SPECT, and coronary artery disease that was not amenable to revascularization. All were receiving maximal medical therapy at five National Heart, Lung, and Blood Institute-sponsored Cardiovascular Cell Therapy Research Network (CCTRN) sites between April 29, 2009 and April 18, 2011.

A total of 92 patients (82 men; average age 63 years) were randomized (n=61 in the BMC group and n=31 in the placebo group) to receive bone marrow aspiration and transendocardial injection of 100 x 10^6 bone marrow cells or placebo.

Changes in LV end systolic volume index (-0.9 mL/m^2 [95% CI, -6.1 to 4.3]; p=0.73), maximal oxygen consumption (1.0 [95% CI, -0.42 to 2.34]; p=0.17), and the difference in the change for percent reversible defect (-1.2 [95% CI, -12.5 to 10.12]; p=0.84) were not statistically significant. No differences were observed in any of the secondary outcomes, including percent myocardial defect, total defect size, regional wall motion, and clinical improvement.

An exploratory analyses revealed that LVEF improved in the BMC group compared with the placebo group (+1.4 vs -1.3; p=0.030). LVEF improvement was observed in patients who were younger than the median study population age and correlated with the percentage of CD34+ and CD133+ cells in bone marrow samples. A prespecified analysis of cell function (ECFC) also showed significant improvement in $MV0_2$ in patients with higher-than-median ECFC values.

Dr. Perin concluded that evaluation of the inherent variability in the cell product may provide mechanistic insights and help select patients who are likely to benefit from autologous cell therapy. He said that additional analyses of cell function will be forthcoming from the CCTRN biorepository and should help guide the design of future clinical trials in patients with ischemic heart disease and LV dysfunction.

The lack of efficacy that was observed in the primary and secondary results is disappointing for this highly anticipated therapy. It is possible that prior smaller studies overestimated the efficacy or that the characteristics of the cell population or delivery system were not optimal in FOCUS-CCTRN. Additional analyses from this study will be helpful in guiding future trials of cell therapy.