Efficacy and safety of lipid lowering by alirocumab in chronic kidney disease

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Peter P. Toth[1], Jamie P. Dwyer[2], Christopher P. Cannon[3], Helen M. Colhoun[4], Daniel J. Rader[5], Ashish Upadhyay[6], Michael J. Louie[7], Andrew Koren[8], Alexia Letierce[9], Jonas Mandel[9,10] and Maciej Banach[11]

[1]CGH Medical Center, Sterling, Illinois, USA; and Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [2]Vanderbilt University School of Medicine, Nashville, Tennessee, USA; [3]Harvard Clinical Research Institute, Boston, Massachusetts, USA; [4]University of Edinburgh, Edinburgh, UK; [5]Perelman School of Medicine, Smilow Centre for Translational Research, Philadelphia, Pennsylvania, USA; [6]Section of Nephrology, Boston University School of Medicine, Boston, Massachusetts, USA; [7]Regeneron Pharmaceuticals, Inc., Tarrytown, New York, USA; [8]Sanofi, Bridgewater, New Jersey, USA; [9]Sanofi, Chilly-Mazarin, France; [10]IviData Stats, Levallois-Perret, Paris, France; and [11]Department of Hypertension, Medical University of Lodz, Lodz, Poland

Individuals with chronic kidney disease are at increased risk of premature cardiovascular disease. Among them, many with elevated low-density lipoprotein cholesterol (LDL-C) are unable to achieve optimal LDL-C on statins and require additional lipid-lowering therapy. To study this, we compared the LDL-C-lowering efficacy and safety of alirocumab in individuals with hypercholesterolemia with impaired renal function, defined as eGFR 30–59 ml/min/1.73 m^2, to those without impaired renal function eGFR ≥60 ml/min/1.73 m^2. A total of 4629 hypercholesterolemic individuals without or with impaired renal function, pooled from eight phase 3 ODYSSEY trials (double-blind treatments of 24–104 weeks), were on alirocumab 150 mg or 75/150 mg every two weeks vs. placebo or ezetimibe. Overall, 10.1% had impaired renal function and over 99% were receiving statin treatment. Baseline LDL-C in alirocumab and control groups was comparable in subgroups analyzed. LDL-C reductions at week 24 ranged from 46.1 to 62.2% or 48.3 to 60.1% with alirocumab among individuals with or without impaired renal function, respectively. Similar reductions were observed for lipoprotein (a), non-high-density lipoprotein cholesterol, apolipoprotein B, and triglycerides. Safety data were similar in both treatment subgroups, regardless of the degree of CKD. Renal function did not change over time in response to alirocumab. This *post hoc* efficacy analysis is limited by evaluation of alirocumab treatment effects on renal and lipid parameters by serum biochemistry. Thus, alirocumab consistently lowered LDL-C regardless of impaired renal function, with safety comparable to control, among individuals with hypercholesterolemia who nearly all were on statin treatment.

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Correspondence: *Peter P. Toth, CGH Medical Center, 101 East Miller Road, Sterling, Illinois 61081. E-mail: Peter.Toth@cghmc.com*

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Chronic kidney disease (CKD), characterized by impaired renal function (IRF), is associated with an increased risk of cardiovascular disease (CVD),[1–3] and a mixed dyslipidemia phenotype: elevated levels of triglycerides and remnant lipoproteins, and reduced levels of high-density lipoprotein cholesterol (HDL-C).[1] Individuals with CKD and elevated low-density lipoprotein cholesterol (LDL-C) are categorized as being at very high risk of CVD.[2,4] Statins are widely prescribed to lower LDL-C in those with CKD and have been shown in numerous large trials to reduce LDL-C levels and cardiovascular (CV) events (except in those on dialysis).[1,2,4–11] However, clearance of most statins is affected by renal function, and most individuals with CKD are on multiple drugs to treat other conditions (e.g., hyperglycemia, hypertension), raising the propensity for drug-drug interactions. Recent treatment guidelines for kidney disease recommend lower doses of statins, hence limiting the use of high-dose statins in those with CKD.[1,2,11–13] Therefore, if further LDL-C reduction is required, additional lipid-lowering therapies may be needed. The American College of Cardiology expert consensus decision pathway recommends the addition of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors or ezetimibe to maximally tolerated statin therapy in high-risk patients with atherosclerotic CVD and CKD with <50% LDL-C reduction on statins, including high-intensity statins.[14]

Alirocumab is a monoclonal antibody to PCSK9 that reduces LDL-C levels significantly among high to very high risk individuals, including those with very high baseline LDL-C.[15,16] In the phase 3 ODYSSEY clinical program among individuals with hypercholesterolemia, alirocumab reduced LDL-C levels by up to 61% compared with controls and was

generally well tolerated.[15,17] PCSK9 is expressed transiently in the kidneys and may play a role in kidney development.[18] Increased plasma PCSK9 levels are observed in disorders of the glomerular filtration barrier, such as in individuals with nephrotic syndrome.[19,20] Further, a reduction in PCSK9 levels observed during remission in these individuals correlated with decreased levels of atherogenic lipids, suggesting that reducing PCSK9 may treat dyslipidemia in those with kidney disease.[19] Therefore, it is important to evaluate the safety and efficacy of alirocumab among individuals with IRF. The aim of this analysis was to determine the lipid-lowering efficacy and safety of alirocumab among individuals with or without IRF and to assess the impact of alirocumab on renal function over time.

RESULTS

IRF analysis (pool of 8 trials)

Overall, 10.5% (315/3010) of individuals randomized to alirocumab and 9.4% (152/1619) of those randomized to control were categorized as having IRF. The number of individuals with IRF from each of the 8 trials is shown in Table 1. In the subgroups with and without IRF, baseline characteristics were similar between the alirocumab and control groups (Table 2). Individuals with IRF had a mean estimated glomerular filtration rate (eGFR) of 51 ml/min per 1.73 m^2 in both treatment groups, indicating that, on average, these patients had slightly to moderately decreased renal function, belonging to CKD category G3a per CKD treatment guidelines.[2] Individuals with IRF were slightly older and had a higher incidence of diabetes at baseline compared with those without IRF. Baseline levels of LDL-C, non–HDL-C, and apoB were lower among individuals with versus those without IRF, and there was a lower proportion of individuals with IRF with heterozygous familial hypercholesterolemia (Table 2). Individuals with IRF had higher levels of triglycerides and lipoprotein (a) (Lp[a]) at baseline compared with those who did not have IRF. A lower proportion of individuals with versus without IRF were receiving high-intensity statin treatment (40–80 mg atorvastatin, 20–40 mg rosuvastatin, or 80 mg simvastatin [Table 2]).

Efficacy by IRF status

Efficacy was analyzed among individuals with versus without IRF in 3 pools by alirocumab dose and control. In the placebo-controlled pool with alirocumab at a starting dose of 75 mg every 2 weeks (Q2W), 20% (11/55) of individuals with versus 35.9% (217/605) without IRF had their alirocumab dose increased to 150 mg Q2W. In the ezetimibe-controlled pool with alirocumab starting at 75 mg Q2W, 11.4% (8/70) of individuals with versus 18.5% (104/561) without IRF were increased to the higher dose of 150 mg Q2W.

Table 1 | Trials included in this analysis

Comparison	Study	Duration (wk)	Background therapy	IRF,[a] *N* (%)		Without IRF,[a] *N* (%)	
				Alirocumab	Control[b]	Alirocumab	Control[b]
8 trials included in the IRF analysis				*N* = 315	*N* = 152	*N* = 2695	*N* = 1467
Alirocumab 150 mg Q2W versus placebo	LONG TERM[17] (NCT01507831)	78	Maximally tolerated statin[c] ± other LLT	176 (55.9)	74 (48.7)	1377 (51.1)	714 (48.7)
	HIGH FH[16] (NCT01617655)	78		4 (1.3)	1 (0.7)	68 (2.5)	34 (2.3)
	LONG TERM + HIGH FH			180 (57.1)	75 (49.3)	1445 (53.6)	748 (51.0)
Alirocumab 75/150 mg Q2W versus placebo	FH I[35] (NCT01623115)	78		20 (6.3)	9 (5.9)	303 (11.2)	154 (10.5)
	FH II[35] (NCT01709500)			2 (0.6)	1 (0.7)	165 (6.1)	81 (5.5)
	COMBO I[36] (NCT01644175)	52		37 (11.7)	24 (15.8)	172 (6.4)	83 (5.7)
	FH I + FH II + COMBO I			59 (18.7)	34 (22.4)	640 (23.7)	318 (21.7)
Alirocumab 75/150 mg Q2W versus ezetimibe	COMBO II[37] (NCT01644188)	104	Maximally tolerated statin (no other LLT allowed)	61 (19.4)	23 (15.1)	418 (15.5)	218 (14.9)
	OPTIONS I[38] (NCT01730040)	24	Stable statin dose[d] ± other LLT	7 (2.2)	14 (9.2)	97 (3.6)	88 (6.0)
	OPTIONS II[39] (NCT01730053)	24		8 (2.5)	6 (3.9)	95 (3.5)	95 (6.5)
	COMBO II + OPTIONS I + OPTIONS II			76 (24.1)	43 (28.3)	610 (22.6)	401 (27.3)
Additional 2 trials included in the renal safety analysis (10 trials total)				*N* = 321	*N* = 160	*N* = 2867	*N* = 1635
Alirocumab 75/150 mg Q2W versus ezetimibe	MONO[40] (NCT01644474)[e]	24	No statins ± other LLT	0	0	52 (1.8)	51 (3.1)
	ALTERNATIVE[41] (NCT01709513)[e]	24		6 (1.9)	8 (5.0)	120 (4.2)	117 (7.2)
	MONO + ALTERNATIVE			6 (1.9)	8 (5.0)	172 (6.0)	168 (10.3)

eGFR, estimated glomerular filtration rate; IRF, impaired renal function; LLT, lipid-lowering therapy; Q2W, every 2 weeks.
[a]IRF was defined based on medical history: IRF (eGFR: 30–59 ml/min per 1.73 m^2); without IRF included individuals with eGFR: 60–89 ml/min per 1.73 m^2, and normal kidney function (eGFR: ≥90 ml/min per 1.73 m^2).
[b]Control was placebo in 5 trials (LONG TERM, FH I and II, HIGH FH, and COMBO I) and ezetimibe in 3 trials (COMBO II and OPTIONS I and II).
[c]Maximally tolerated statin was defined as atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg daily unless there was an investigator-approved reason for using lower doses (e.g. intolerance).
[d]Atorvastatin 20–40 mg in OPTIONS I and rosuvastatin 10–20 mg in OPTIONS II.
[e]Individuals from MONO and ALTERNATIVE were included only in the analyses of renal function over time.