PCSK9: the Critical Role of Familial Hypercholesterolemia from Discovery to Benefit for all

Editorial to: “Efficacy and Safety of Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia and LDL-C of 160 mg/Dl or Higher” by Henry N. Ginsberg et Al.

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Yet again familial hypercholesterolemia (FH) has lead the way in developing new therapies to reduce cardiovascular disease (CVD) by providing the discovery and biology of PCSK9 and its relationship to LDL cholesterol (LDL-C) metabolism. This discovery has rapidly resulted in another new and effective therapy that will likely benefit not just FH but a broad spectrum of high-risk patients. Since the initial description of FH in 1938 by Muller [1] which provided the closest and most plausible link that cholesterol, ultimately LDL-C, was causative in CVD, FH patients have played a central and critical role in every advance in the understanding of LDL-C metabolism, development of new therapies and validation that decreasing LDL-C reduces the progression of coronary atherosclerosis and lowers morbidity and mortality from CVD [2–12]. Commencing with the studies by Brown and Goldstein, FH played a paramount role in identifying both the LDL receptor (LDLR) and the rate limiting step in cholesterol synthesis, HMG CoA reductase, and in turn the role of this key enzyme in regulating LDLR activity [2–4]. These investigations rapidly led to a search for, and the discovery of, inhibitors (‘statins’) of the enzyme, with FH, especially heterozygous FH (HeFH) again playing a vital role in their early development [5]. Even prior to the discovery of the LDLR and the importance of HMG CoA reductase, FH had been pivotal in developing therapies to reduce LDL-C via bile acid diversion that began in the mid 1960s with ileal bypass surgery and later drugs which sequestered bile in the gut from reabsorption [6, 7]. Over the last 50 years FH has been involved in the proof of

concept and developmental trials for virtually all LDL-C lowering therapies, including apheresis and ‘LDLR gene replacement’ via hepatic transplant, that have been approved, and many that were not. In fact, it would be fair to state that if a LDL-C lowering therapy works in FH it will work in everyone.

While no CVD outcome trials specifically enrolling HeFH patients have been carried out, there are a number of, both primary and secondary prevention trials where HeFH patients have likely formed the bulk of the enrolled populations [7, 9–12]. These trials are shown in Table 1 and highlights that just 30 years ago the LDL hypothesis was considered so unproven that it was possible, and considered ethical, to randomize HeFH patients, even with CVD, to long term placebo controlled trials. These trials especially the NIH funded Coronary Primary Prevention Trial (CPPT), which formed the basis for first American National Cholesterol Education Program Adult Treatment Panel guidelines (NCEP-ATP I), and the Scandinavian Simvastatin Survival Study (4S) which changed cardiology forever, owe their success to the many HeFH patients who experienced increased morbidity and mortality on placebo for 5 to 10 years. In retrospect the trials also provide probably the best, and only prospective, data on the high risk of CVD events in nearly 8000 untreated, mostly male, HeFH patients. The annual rate of major cardiovascular events, such as CVD death or myocardial infarction (MI) in these relatively young FH patients with pre-existing atherosclerotic disease in the secondary prevention trials of 5–6 % and nearly 2 % in the primary prevention trials of middle aged men carefully screened to exclude those with other risk factors and CVD at entry, reinforces the need to both identify and aggressively treat FH as early as possible. Even in the groups receiving the active treatment in these trials, where LDL-C reductions of 20–35 % were attained, the CVD morbidity and mortality, while reduced, was very high.

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Table 1 Cardiovascular intervention or outcome trials where FH patients played significant role

Trial	Type	Treatment	number	Age: yrs	Gender	Trial design	Baseline LDL-C mg/dL (mean)	Annual CVD event rate in placebo or control group	CVD rate in Rx grp
Type II CIS ⁺	Secondary/ angiography	BAS*	143	46	81 % male	Randomized placebo controlled	236**	CVD death or MI = 3.3 %	2.7 %
POSCH [‡]	secondary	Partial Ileal Bypass	838	51	91 % male	Randomized open label	179	CVD death, MI, UA = 5.8 %	4.2 %
CPPT [¶]	primary	BAS*	3806	48	100 % male	Randomized placebo controlled	205**	MCE [¶] = 1.8 %	1.6 %
4S [#]	secondary	Simvastatin	4444	58 ^Δ 60.5 ^{ΔΔ}	82 % male	Randomized placebo controlled	188**	MCE [¶] = 5.2 %	3.6 %
WOSCOPS	primary	Pravastatin	6595	55.2	100 % male	Randomized placebo controlled	192	CVD death or MI = 1.6 %	1.1 %

* National Institutes of Health Type II Coronary Intervention Study [7] * bile acid sequestrant (cholestyramine) **after diet

[‡] Program on the Surgical Control of the Hyperlipidemias [9] ^Δ males ^{ΔΔ} females

[¶] The Lipid Research Clinics Coronary Primary Prevention Trial [10] [¶] major coronary events = CV death, definite/probable MI, resuscitated cardiac arrest

[#] Scandinavian Simvastatin Survival Study [11]

These trials served to help obtain regulatory approval for LDL-C lowering treatments, drive development of national and global guidelines for prevention of CVD and have resulted in LDL-C reduction becoming the mainstay to reduce the CVD burden in the general population, but there has remained a large treatment gap for FH patients.

The discovery in 2003 of PCSK9, once again in patients with FH, and the rapid elucidation of its role in regulating the LDLR and plasma LDL-C has produced the most exciting and promising therapy in the last 3 decades [13–15]. This therapy is of even greater potential benefit for FH patients, especially when combined with existing therapies of statins and ezetimibe as highlighted in the publication by Ginsberg et al. [16] from the ODYSSEY High FH trial in patients with severe HeFH. Just as for statins, FH patients have been prominent in the initial and subsequent development programs of the two recently approved PCSK9 monoclonal antibody (mAb) inhibitors, alirocumab and evolocumab. Unlike prior LDL-C lowering drug development FH patients were included in even the phase 1, multiple ascending dose studies, establishing very early that not only did FH patients respond with dramatic reductions in LDL-C but that they had the same response as nonFH patients [15, 17]. Since these early proof-of-concept studies more than 1800 HeFH, with a wide array of different LDLR defects Apo B and PCSK9 gain of function mutations, have been included in the phase 2 and 3 trials as summarized in Table 2 [18–22]. Furthermore numerous other FH patients, not separately identified as such, were included in the trials of statin adverse patients, GAUSS, GAUSS-2, GAUSS-3 and ODYSSEY Alternative [23–26], where mean baseline LDL-C were >190 mg/dL. The large number of FH patients participating in these trials almost certainly reflects the unmet need, and pent up demand, for more effective LDL-C reduction in FH.

The ODYSSEY High FH trial results, are generally consistent with the larger more robust FH trials preceding it (Table 2), and while admirable in its intent to assess the effectiveness of PCSK9 inhibition in a more severe group of HeFH patients with LDL-C > 160 mg/dL on maximal drug therapy, suffered from a number of unfortunate and unforeseen problems, especially for a relatively small trial, but also raise a number of other concerns. A total of 72 patients were randomized to alirocumab 150 mg every 2 weeks (Q2W) but only 60 % completed the 78 week trial, with 26 % discontinued at 3 sites which failed to comply with acceptable clinical trial practices. Another 14 % terminated for a variety of reasons, mostly unrelated to tolerability or safety. This contrasts significantly with the previous alirocumab FH trials such as FH I and II of similar duration, and FH trials in general where adherence rates are uniformly good, even in pediatric populations, due to the highly motivated patient populations. The patients in High FH while of similar age, gender and CVD disease prevalence, was discordant with

Table 2 PCSK9 Phase 2/3 randomized placebo controlled trials with alirocumab and evolocumab in FH patients on maximal tolerated statin therapy with/without ezetimibe

Trial (reference)	Type	Treatment	N	Age: yrs	Gender	mean LDL-C at baseline	Treatment duration	Discon rate (%)	DM [¶]	% (absolute) LDL-C dec ^Δ	% CVD events Rx/PBO
REGN 727 HeFH ¹⁸	Phase 2	alirocumab* 150 mg Q2W or 300 mg Q4W	77	53	61 % male	147 mg/dL	12 weeks	1.3 %	4 %	57 % (84 mg/dL)	0/0
RUTHERFORD ¹⁹	Phase 2	Evolocumab 350/420 mg Q4W	168	49	53 % male	158 mg/dL	12 weeks	4.2 %	4 %	56 % ^Δ (85 mg/dL)	0/0
RUTHERFORD-2 ²⁰	Phase 3	Evolocumab 140 mg Q2W or 420 mg Q4W	331	51	58 % male	154 mg/dL	12 weeks	1.1 %	7 %	60 % (93 mg/dL)	1.4/0
ODYSSEY FH I ²¹	Phase 3	Alirocumab 75/150 mg Q2W	486	52	56 % male	144 mg/dL	78 weeks [‡]	22 %	12 %	58 % (84 mg/dL)	2.5/1.8
ODYSSEY FH II ²¹	Phase 3	Alirocumab 75/150 mg Q2W	249	53	53 % male	134 mg/dL	78 weeks [‡]	11 %	4 %	51 % (69 mg/dL)	1.2/1.2
ODYSSEY High FH ¹⁶	Phase 3	Alirocumab 150 mg Q2W	107	51	53 % male	200 mg/dL	78 weeks [‡]	36 %	14 %	39 % [⊗] (75 mg/dL)	8.3/0
ODYSSEY Long-term FH ²²	Phase 3	Alirocumab 150 mg Q2W	415	60*	62 % male*	NPS	78 weeks	27 % [#]	NPS	NPS 44 %** (94 mg/dL)	NPS

[#] all patients as FH not separate data ^Δ placebo adjusted with approved doses (75 mg or 150 mg Q2W or 420 mg Q4W evolocumab)

^{*}all patients as FH data not provided separately [⊗] 50 % excluding discontinued sites [‡]primary end point for LDL-C at 24 weeks [¶]type 2 diabetes

^{**}In 156 patients with baseline LDL-C > 160 mg/dL NPS not provided separately

prior trials in regard to use of ezetimibe with only 19 % in the alirocumab group on the drug, somewhat counter to expectations in HeFH patients unable to reduce their LDL-C below 160 mg/dL on statin alone. In addition as recently confirmed by Besseling et al. in a large study in Holland, diabetes is uncommon in FH and even less common in the more severe FH with LDLR negative mutations [27]. Thus, it is surprising that there were 14 % diabetics in the trial, which was also a larger number than in any of the prior FH trials.

The placebo adjusted mean reduction in LDL-C from baseline, based on an ITT analysis at primary end point of week 24 was 39 %, and from Fig. 2 only 35 % at the end of the 78 week treatment phase. This obviously reflects the high discontinuation rate in the early part of the trial. The sensitivity analysis excluding patients from the three non-compliant sites resulted in a placebo adjusted mean reduction from baseline of 50 %, was more consistent, but still lower, than other trials in HeFH where doses of alirocumab 150 mg Q2W or evolocumab 140 mg Q2W or 420 mg Q4W, known to fully suppress PCSK9 and obtain maximal LDL-C reductions, were used. The higher baseline LDL-C should also have resulted in as much, if not greater, absolute LDL-C reduction but did not. While accepting the impact of the high discontinuation rate on efficacy it does however raise the question as to the LDL-C response seen in patients with higher baseline LDL-C levels, as initially raised in the ODYSSEY Long-term analysis of decrement by baseline LDL-C [22]. In a post hoc analysis Robinson et al. assessed the LDL-C response in large cohorts of patients with baseline LDL-C of <100, 100–129, 130–159 and ≥160 mg/dL and after adjustment for placebo they reported mean LDL-C reductions of 75 %, 63 %, 55 % and 41 % respectively in the groups. The most similar comparisons to High FH, based on baseline LDL-C would be trials with PCSK9 mAbs involving statin adverse patients [23–26]. The patients, on no or minimal statin or other lipid lowering therapy, had baseline LDL-C of 191 mg/dL in ODYSSEY Alternative, 193 in both GAUSS and GAUSS-2 and 220 mg/dL in GAUSS-3, and while due to study design none could be placebo adjusted, had LDL-C reductions of 52 % (96 mg/dL), 51 % (91 mg/dL), 55 % (106 mg/dL) and 53 % (103 mg/dL) respectively. In ODYSSEY Alternative trial only about half the patients were on 150 mg Q2W dosing and the reductions of 52 % are the secondary efficacy endpoint reflecting only patients who completed treatment. However the absolute LDL-C reductions in all these trials were very robust and in fact larger than the reductions seen in the HeFH trials where the percent decreases were greater but, due to lower baseline LDL-C, the absolute reductions were lower. Thus based on the 50 % LDL-C reduction seen in the sensitivity analysis of High FH which is more consistent, even if at the lower end, with the trials with much higher baseline LDL-C it suggests that while there may be less percent reduction in LDL-C in these patient groups the absolute LDL-C

reductions, which is the key driver of CVD risk reduction, is enhanced.

The final concern raised by High FH is the CVD events of 8 % in the alirocumab group compared to 0 % in placebo. The authors rightly discuss that such imbalances in small trials with very few CVD events are not uncommon, and as shown in Table 2 similar imbalances unfavorable to PCSK9 mAb treatment have been seen, although to a lesser extent and involving even few patients; in RUTHERFORD-2 (1.4 % versus 0 %) and ODYSSEY FH I (2.4 % versus 1.8 %) and also in other high baseline trials GAUSS-3 (1 % versus 0 %) and ODYSSEY Alternative (2.4 % versus 1 %). The two larger and longer recently reported trials, OSLER and ODYSSEY Long-term, which did include HeFH patients, reported in an exploratory and post hoc analysis of CVD events favorable and statistically significant reductions with evolocumab and alirocumab compared to control or placebo respectively, and hopefully the large CVD outcome trials currently in progress and exceeding 70,000 patients will contain enough FH like patients with high baseline LDL-C levels to clarify this concern [22, 28, 29]. However, it would be optimal, and probably ethical given that many FH patients will not routinely receive these therapies due to cost, to perform a CVD outcome trial in HeFH, and nonFH patients with LDL-C > 130 or >160 mg/dL, after treatment with maximally tolerated statins plus ezetimibe and include those with and without CVD.

It is however fitting that PCSK9 mAb treatment, which originated from the discovery in very rare FH patients, has come full circle to now directly benefit patients with far more common forms of FH, both HeFH and even the rarer homozygous (Ho) FH [30]. The addition of PCSK9 inhibitors to statins and ezetimibe finally provide physicians and patients with the therapies needed to achieve LDL-C levels in virtually all HeFH and many HoFH only dreamt of a decade ago. If started early enough in life the combination of these drugs should drastically reduce or even eliminate the early mortality and morbidity in the tens of millions of FH patients now known to have this lethal genetic disorder worldwide [31].

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