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Use of the PCSK9 inhibitor, evolocumab, in patients with heterozygous familial hypercholesterolemia

Abstract

Evolocumab is a monoclonal immunoglobulin G2 that acts against human proprotein convertase subtilisin/kexin type 9 (PCK9) used against Homozygous familial hypercholesterolemia and Heterozygous familial hypercholesterolemia in high cardiovascular disease risk patients with increased level of triglycerides. Evolocumab is administered subcutaneously 420mg every month and 140 mg twice a week in patients with HeFH as evaluated by RUTHERFORD and RUTHERFORD 2 trials. This paper reviews the six clinical trials of evolocumab that evaluated the efficacy of the drug for heterogenous familial hypercholesterolemia.

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Introduction

The papers address clinical trials of Evolocumab, which acts against human proprotein convertase subtilisin/kexin type 9 (PCSK9) which is a monoclonal immunoglobulin G2 used for the treatment of homozygous familial hypercholesterolemia, heterozygous familial hypercholesterolemia, in high cardiovascular risk diseases due to increased level of triglycerides.[1]Evolocumab is an effective and safe drug when prescribed for subcutaneous administration 420mg every month and 140mg twice a week in patients with HeFH as demonstrated by phase 2 of RUTHERFORD and phase three of RUTHERFORD–2 trials.[2] The Six studies published between 2008 and 2017 on the efficacy and safety of evolocumab in heterozygous familial hypercholesterolemia are reviewed in this paper.

The six studies providing_the data on efficacy and safety of evolocumab in heterozygous familial hypercholesterolemia (HeFH) are:

a. phase three study that assessed evolocumab in HeFH patients with Low Density Lipoprotein cholesterol range of 2.6 mmol/L or above,[3]

b. phase 2 study in cardiovascular atherosclerosis patients administered with lipid reduction intervention,[4]

c. comparison study analysing greater efficacy of evolocumab,[5]

d. phase 2 study looking effect of evolocumab after twelve weeks of administration,[6]

e. Two studies assessing evolocumab in patients who had undergone parent trial.[7–8]

Studies assessing the effect of evolocumab on ldl

Phase 3 study of hefh patients having ldl level of 2.6mmol/l or above

A placebo-controlled, multicentre, double-blind, randomized, phase three study evaluating the safety and efficacy of evolocumab in HeFH with LDL concentrations of 2.6mmol/L or above. This trial is globally the largest of clinical trials evaluating the effect of evolocumab in HeFH.[3] Patients (n=331) were randomly assigned to receive evolocumab subcutaneously (SC) 140mg biweekly (n=111), 420mg every month (n=110), placebo biweekly (n=55), or placebo every month for 12weeks (n=55) in the ratio of 2:2:1:1. The cohort was classified on the basis of LDL level (above or below than 4·1 mmol/L) at screening and ezetimibe baseline usage (Yes/No) (Table 1).[3]

In comparison to placebo, administration of evolocumab biweekly lead to in mean reduction in LDL level at the end of twelve weeks of 59.2% (95% CI 53.4–65.1) and reduction at the end of mean of weeks ten and twelve of 60.2% (54.5-65.8) (both p<0.0001). 420mg administered monthly lead to reduction in mean LDL cholesterol of 61.3% (53.6-69.0) at the end of week 12 and at the mean of end of weeks 10 and 12 of 65.6% (59.8-71.3) (both p<0.0001). Reduction in LDL cholesterol measured at the end of two weeks remained constant through twelve weeks and was not found to be associated with sex, age, body-mass index, statin concentration, concomitant use of ezetimibe, or level of LDL at screening. 68% in 140mg dosed every two weeks group and 63% in 420mg every month group had their cholesterol concentration lowered by 1.8mmol/L at end of week twelve as in comparison to placebo group. The mean of end of weeks ten and twelve also had parallel effects (p<0.0001). At the end of week 12, the mean reductions in apolipoprotein and lipoprotein (a) were significant in the drug group compared to placebo groups. The triglyceride concentration reduced significantly in the 140mg biweekly group in comparison with the placebo group while the 420mg monthly evolocumab group had smaller but significant reduction in triglyceride. There was significant increase in HDL cholesterol in both the groups compared to the placebo groups.[3]

At week 12, the mean reduction in negative activity of LDL receptor were 61% (95% CI 45-77) for 140mg biweekly and 55 % for the 420mg monthly group: in receptor defective activity group there was 49% and 66% reduction respectively; and 62 % and 63 % in unclassified LDL receptor patients (p=0.16 for the biweekly group and p=0.68 for the every month group–interaction). In genetically confirmed familial hypercholesterolemia decrease in LDL cholesterol at week 12 were 64% (95% CI 38–39) in140mg–two weeks group and 43 % (28–59) in 420mg every month group. c.313+1G>A mutation patients assigned randomly to the drug had LDL levels in the range of 27% to 83%. Patients with genetic homozygotes or compound heterozygotes had mean reduction at week 12 of 48 % (38-64) for

the 420mg every month group and 68 % (40-82) in 140mg every 2weeks. The mean reduction in LDL cholesterol with apolipoprotein B mutations at the end of week twelve were 50 % (36–65) with 420mg every month group and 51% (35–64) with evolocumab 140mg every 2weeks. At the end of week 12 the mean reduction in apolipoprotein B were 42% to 53% and were similar in LDL receptor negative activity, unclassified LDL receptor, LDL receptor defective activity, and in no mutation identified for both dosing schedules (interaction p=0.88 for every two weeks group and p=0.70 for the every month group).[3]

Adverse events reported were neurocognitive effects, anti–evolocumab, abnormal laboratory values and cardiovascular events which were similar in evolocumab and placebo groups and in the previous studies of evolocumab. Nasopharyngitis was reported for 9% in the drug group and 5% in the placebo group. Muscle related events accounted for 5% in the drug group and 1% in the placebo group. No adverse events were in association with evolocumab. None of the events led to discontinuation of the study drug.[3]

Table 1 Key inclusion and exclusion criteria, and primary, and secondary endpoints

Key inclusion criteria	Patients 18-80 years of age
	Diagnosis of heterozygous familial hypercholesterlemia
	Stable dose of statin with or without lipid modifying therapy for at least 4 weeks before screening
Key exclusion criteria	Homozygous familial hypercholesterolemia
	Patients who had undergone lipoprotein apheresis within previous 4 months
	LDL cholesterol <2-6 mmol/L
	No stable dose of statin
	Diabetes
	Liver disease
	On prohibited lipid-regulating medication
	Malignancy with previous 5 years
	Recent myocardial infarction or stroke
	Hyperthyroidism or Hypothyroidism
Co-primary endpoints	Percentage change in plasma LDL cholesterol from baseline to week12 and at the mean of weeks 10 and 12
secondary endpoints	The absolute change from baseline in LDL cholesterol and the percentage of patients whose LDL cholesterol lowers below 1,8 mmol/L at the same time points
	The mean percentage change in other lipids, apolipoprotiens, high

LDL, low density lipoprotein; **mmol**/L, millimoles per litre

Phase 2 study evaluating the efficacy and safety of evolocumab

This double-blind, multicenter, randomized, 52–week placebo controlled trial assessed the safety and efficacy of 52 weeks of the drug that included 139 patients (mean age, 59 years) with atherosclerosis cardiovascular disease who were receiving background therapy of atorvastatin 80mg with or without ezetimibe 10mg daily. The patients were randomized to placebo or to evolocumab 420mg once every month.[4]

The percent baseline change in the LDL level at week 52 in the group receiving the drug as compared to those in the placebo group is the primary end point. In addition, the primary efficacy group was measured. The secondary efficacy endpoint was the absolute baseline change in the LDL level at the end of week 52, the percent change baseline change in LDL level at the end of week 12 and the percentage of patients who had LDL below 70mg/deciliter. Adverse events, laboratory tests, clinical examination were assessed for evaluating the safety of the drug.

The baseline least squares mean reduction in LDL level in the evolocumab group was 57.0=-2.1% at week 52 and 57.5=-1.6% at week 12. The least mean square reduction in LDL level in the drug group, in the background therapy group, and in the placebo group was 48.5±5.2% in the group receiving atorvastatin 80mg along with ezetimibe 10mg, 56.8±5.3% in the atorvastatin 80mg group, 61.6±2.6% in the atorvastatin 10mg group, and 55.7±4.2% in the diet alone group.[4]

Adverse events encountered were similar in the drug (74.8%) and the placebo (74.2%) group. Adverse events in the drug group were influenza, back pain, nasopharyngitis and upper respiratory tract infection. 5.5% in the drug group and 4.3% in the placebo group experienced serious adverse events. Discontinuation of study occurred in 2.2% of the drug group and 1% in the placebo group. Injection site reactions occurred in 5.7% in the drug group and 5% in the placebo group. The drug did not affect glycemic index. None of the patients were detected with anti-evolocumab neutralizing antibodies.[4]

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Study assessing the effect of evolocumab on ldl levels in hefh patients withdrawing from regular apheresis

A study evaluated the effect of evolocumab in HeFH and its association with the regular LDL apheresis.[5] Patients (n=11) were assigned to subcutaneous injection of evolocumab 140mg twice a week who were previously undergoing biweekly LDL apheresis. The primary endpoints were percentage change in mean apolipoprotein B (apoB) serum levels and LDL–C. Due to the switch in the treatment the primary endpoints were the average of two different time point measurement.[5]

The mean reduction in LDL–C from 2.55±0.62 mmol/L to 0.96±0.40 mmol/L (-62.5%, p<0.0001) and the reduction in apo B from 82.8 ± 12.3mg/dL to 45.4 ±10.9mg/dL (-45.2%, p<0.0001) were significant. Reduction in serum lipoprotein from 148 (116-351) mg/L to 91 (53–289) mg/L (-38.5%, p<0.01) were significant. Even though serum vitamin E levels reduction in patients assigned to evolocumab were significant, it was still within normal range. No adverse events were reported with evolocumab.[5]

Evolocumab injection therapy is less invasive, less expensive, consumes less time and is more effective in reducing atherogenic lipoprotein levels without causing any adverse side effects HeFH as compared to LDL apheresis.[5]

Study assessing the level of ldl–c in hefh patients

A placebo controlled phase 2 (RUTHERFORD) double-blinded, multicenters, global trial evaluated the effect of 12weeks of AMG 145 administered subcutaneously every 4weeks on the percentage change in LDL–C in HeFH. The trial evaluated the tolerability and safety of evolocumab and the absolute change in LDL–C, percentage change in non HDL levels, ApoB, total cholesterol/HDL–C ratio, and ApoB/apolipoprotein A1 ratio (Table 2).[6]

Table 2 Inclusion and exclusion criteria

Inclusion criteria	**Male or female≥18 to≤75 years of age**
	Diagnosis of heterozygous familial hypercholesterolemia by having met the
	diagnostic criteria outlined by the Simon Broome Register Group (Scientific Steering Committee 1991)
	On an approved statin, with or without ezetimibe, with stable dose(s) for at least 4 weeks
	Fasting Low-Density Lipoprotein Cholesterol (LDL-C) ≥ 100 mg/dL Fasting triglycerides ≤ 400 mg/dL
Exclusion criteria	**Homozygous familial hypercholesterolemia**
	Low-Density Lipoprotein (LDL) or plasma apheresis within 12 months prior to randomization
	New York Heart Association (NYHA) III or IV heart failure, or known left ventricular ejection fraction < 30%
	Uncontrolled cardiac arrhythmia
	Myocardial infarction, unstable angina, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) or stroke within 3 months prior to randomization
	Type 1 diabetes; newly diagnosed or poorly controlled type 2 diabetes (HbA1c > 8.5%)
	Uncontrolled hypertension

LDL, Low Density Lipoprotein; HbA1c, Hemoglobin A1C

Patients (n=168) were randomly assigned to AMG 145 250mg (n=56), AMG 145 420mg (n=56) or placebo (n=56).The baseline percentage change in LDL–C at 12weeks was the primary end point. Secondary end point was the baseline percentage change at week 12 in non-HDL–C, ApoB, total cholesterol/HDL–C ratio, ApoB/ApoA1 ratio and baseline absolute change in LDL-C at week 12.[6]

The percentage reduction in LDL-C (least square mean) was 43% in the AMG 145 350mg and 55% in the 420mg dose groups in comparison to the 1% increase in the placebo group (both doses P<0.001 versus placebo). LDL–C reduction in ezetimibe or statin alone showed similar differences in treatment in comparison to placebo with -44.1% and -54.5% in the statin plus ezetimibe and statin alone group–43.4% and -59.7% for AMG 145 350mg and 420mg respectively. LDL-C reduction at week 2 for both groups were 66% and 73% respectively in comparison with the placebo group, were greater as compared to weeks 4, 8, and 12. LDL-C concentration mean absolute values at week 12 were 2.3 (0.2) for AMG 145 350mg, 1.7 (0.1) for AMG 145 420mg and 4.2 (0.2) for placebo group. Treatment with AMG 145 350mg and 420mg administered every 4weeks led to 70 % and 89% of patients LDL-C reaching levels of <2.6 mmol/L and 44% and 65% attaining <1.8 mmol/L compared with 2% and 0% respectively. Reduction in non-HDL-C, total cholesterol and ApoB were similar to those observed in LDL-C. Significant reduction in free PCSK 9 levels due to AMG 145, and at the end of week 12, at the end of 4weeks after the last dose of AMG 145, reduction in 41% from the baseline was observed. Lower free PCSK9 and lower LDL-C levels were significantly associated at all visits and doses.[6]

In this study, no significant safety findings were observed clinically in the treatment with AMG 145. AMG 145 420mg group had higher incidence of adverse events as compared to the placebo group and AMG 145 350mg group; however none of the adverse event was related to AMG145. Serious adverse events included appendicitis in one patient and atrial fibrillation in other; however they were not treatment related. The three most common adverse events reported for AMG 145 (AMG 145 350mg; AMG 145 420mg; placebo) were nasopharyngitis (12.7%; 12.5%; 10.7%) headache (5.5%, 5.4%; 8.9%) and injection site pain (9.1%; 3.6%; 1.8%).[6]

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The three most common adverse events (AMG 145 350mg; AMG 145 420mg; placebo) were skin burning sensation (1.8%; 3.6%; 0.0%), headache (5.5%, 1.8%; 0.0%) and injection site pain (7.3%; 3.6%; 1.8%). One patient from each of the group experienced adverse events leading to discontinuation of the study drug. In patients on AMG 145 420mg diarrhea, nausea and groin pain were possibly considered to be treatment related and other patient on 350mg discontinued the study drug due to weight gain. Most of the patients on AMG 145 did not encounter any elevation of liver enzymes.2% of the patient in the AMG 145 420mg who experienced asymptomatic elevation in creatinine kinase (>10XULN at week 8). This elevation was caused because of strenuous exercise that resolved naturally without study drug discontinuation. No differences in adverse events were observed between the AMG 145 groups and placebo for–immunogenicity, muscle events, hypersensitivity, injection site reactions, hepatic disorders, transaminase elevations, and hepatitis. None of the study groups of AMG145 were observed to have neutralizing and binding antibodies.[6]

Study evaluating the efficacy of evolocumab in patients with hypercholesterolemia

An open label, global, long term evaluation against LDL–C (OSLER) study conducted to evaluate the efficacy and safety of long term administration of evolocumab in Hypercholesterolemia. This study included patients from one or more of the 4 (RUTHERFORD, MENDEL, GAUSS, and LAPLACE–TIMI 57) phase 2 studies conducted for evolocumab against PCSK9 for reduction of elevated LDL-C.[7]

Patients were randomized to either of the two groups - evolocumab 420mg SC every 4weeks plus standard of care (SOC) (n=736) or SOC alone (n=368) (Table 3).[7]

Patients who had not taken the drug in the parent phase 2 study had a huge initial LDL–C reductions at the end of 12weeks after starting the drug treatment in this study (51.8% [SEs, 1.6%] reduction in terms of parent baseline study; p<0.0001 in comparison to the reduction maintained over the 52week study duration (52.3% [SE, 1.8%] at week 52; p<0.0001 versus Adverse events reported in this study were upper respiratory tract infections, influenza, arthralgia, back pain and nasopharyngitis in both groups. Serious AE's were observed in 6.3 % of patients in the SOC group and 7.1% in the evolocumab plus SOC group. No particular AE's were seen in either of the groups or were considered to be related to evolocumab. 3 % of patients had AE leading to study drug discontinuation. Injection site reaction was observed in 3.8% of patients in the SOC+drug group. Neutralizing antibodies were not detected in this study (Table 4).[7]

Table 3 Efficacy and safety end points

Primary Efficacy objective	To characterize the long term administration effects of evolocumab in patients with hypercholesterolemia as assessed by LDL-C, non-high density lipoprotein cholesterol (non- HDL-C), apolipoprotein (Apo) B, ration of total cholesterol to HDL-C, and ApoB/ApoA1 ratio.
Primary Safety objective	To characterize the safety and tolerability of longer term administration of evolocumab.
Safety End points	Incidence of AE's
	Serious AE's
	AE's leading to discontinuation of investigational product.

HDL, high density lipoprotein baseline

Table 4 Percentage of patients who attained LDL-C goals at follow up OSLER visits

<2.6 mmol/L (100 mg/dL)	**<1.8 mmol/L (70 mg/dL) n(%)**		**n(%)**			
Category (n with LDL-C measurement	**SOC**	**evolocumab 420 mg**	**SOC**	**evolocumab 420 mg in SOC and in evolocumab**	**Every 4 wk + SOC**	**Every 4 wk + SOC 420 mg every 4 week plus SOC)**
At parent end of study	231 (64.4)	491 (68.5)	151 (42.1)	302 (42.1)		
At week 12	60 (17.3)	621 (86.7)	1 (0.3)	443 (61.9)		
At week 24	59 (17.3)	613 (86.6)	3 (0.9)	431 (60.9)		
At week 36	47 (14.0)	598 (85.6)	5 (1.5)	430 (61.5)		
At week 48	43 (16.7)	580 (85.8)	2 (0.6)	415 (61.4)		
At week 52	47 (15.9)	552 (86.3)	3 (1.0)	400 (62.5)		
Met target goal at any baseline visit	117 (32.4)	703 (96.0)	13 (3.6)	606 (82.8)		
Met target goal at all post baseline visit	9 (3.3)	437 (72.1)	0 (0.0)	229 (37.8)		

OSLER, open-label study of long-term evaluation against; LDL–C, SOC, standard of care; P<0.0001 for all comparisons except at parent end of study and evolocumab 420mg every 4 weeks+SOC.[7]

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Study evaluating the efficacy and safety of evolocumab in patients who had completed parent trials

An open label–extension trials that assessed the long term safety, tolerability, and efficacy of evolocumab in HeFH patients who had completed parent trials.[8]

Patients (n=444) who had completed parent [RUTHERFORD (n=147) and RUTHERFORD-2 (n=93)] trials were assigned randomly to 2:1 to evolocumab plus SOC or SOC alone for 52 weeks(Open Label Study of Long term Evaluation Against LDL-C [OSLER-1] or 48weeks (OSLER-2). Dosing was evolocumab 420mg monthly (OSLER-1) and 140mg twice weekly or 420mg monthly (OSLER-2).[8]

In comparison to the baseline parent study, patients who received SOC plus evolocumab showed a mean reduction in 53.6%. Patients receiving evolocumab plus SOC experienced a mean reduction in LDL-C of 53.6% after 48weeks in comparison to baseline parent study. No adverse events were experienced that led to study drug discontinuation. Continuous administration of evolocumab plus SOC in HeFH results in significant reduction in low-density lipoprotein cholesterol at the end of 48weeks. SOC plus long term evolocumab administration was found to be safe and well tolerated. Both the groups experienced serious adverse–evolocumab plus SOC (7.3%) and SOC (8.6%).[8]

Summary

Validity and conclusion of the six studies

Evolocumab administered either 140mg every 2weeks or 420mg monthly was well tolerated by patients with HeFH. The drug yielded rapid and similar LDL cholesterol reductions in comparison with placebo.[3] There was a 57% relative reduction in LDL cholesterol levels in response to treatment with 420 g of evolocumab every 4weeks for 52weeks. The results produced were in line with that observed in 12–week phase 2 trials the same evolocumab regimen. There was also no decrement in the efficacy of evolocumab from week 12 to week 52.[4]The study showed that evolocumab biweekly therapy consumes less time, is less and less expensive and is more successful in the atherogenic lipoprotein levels reduction with side effects.[5]

The study results showed that AMG 145 can help high risk patient population in which 21% had pre existing coronary artery disease and baseline LDL–C>3.9 mmol even with intensive statin use. This study proved that AMG 145 SC Q4W addition to intensive lipid reduction therapy resulted in LDL–C reduction in a dose responsive manner.[6] Fourweeks of dosage of evolocumab exhibited safety, tolerability and efficacy over 1year treatment in the longest and largest PCSK9 inhibitor evaluation in patients with hypercholesterolemia till date.[7]Administration of evolocumab continuous use in addition to SOC in HeFH patients produced consistent and demonstrated reduction in LDL–C levels during 48weeks follow up. Administration of evolocumab with SOC was well tolerated and safe on a long term.[8]

Data assessing the efficacy and safety of evolocumab in HeFH are available from a phase 3 study that evaluated the level of LDL–C in HeFH, a 12weeks phase 2 study gauging the effect of evolocumab therapy, phase 2 study in atherosclerotic CVD patients who had received background lipid lowering therapy, comparison study analyzing the efficacy of evolocumab and two phase 2 studies evaluating the effect of evolocumab in patients who had undergone parent trial.[9]

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Conflict of interest

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