Long-term safety and efficacy of alirocumab in South African patients with heterozygous familial hypercholesterolaemia: the ODYSSEY Open-Label Extension study

Dirk J Blom, Johannes Breedt, Lesley J Burgess, Iftikhar O Ebrahim, Graham Ellis, Prashilla Soma, Eugene van der Walt, Poobalan Naidoo, Alet van Tonder, Frederick J Raal

Abstract

Background: Alirocumab reduces low-density lipoprotein cholesterol (LDL-C) levels by up to 61%. The ODYSSEY Open-Label Extension study investigated the effect of alirocumab in patients with heterozygous familial hypercholesterolaemia (HeFH) over 144 weeks.

Methods: Eligible patients with HeFH had completed an earlier double-blind, randomised, placebo-controlled parent study. Patients were initiated on 75 mg alirocumab Q2W subcutaneous (SC) unless baseline LDL-C was > 8.9 mmol/l, in which case they received 150 mg alirocumab Q2W. Dose titration to 150 mg Q2W was at the investigator's discretion.

Results: The study enrolled 167 patients and the parent study mean (± SD) baseline LDL-C level was 3.65 ± 1.9 mmol/l. Mean LDL-C level was reduced by 48.7% at week 144; mean on-treatment LDL-C was 2.30 ± 1.24 mmol/l. Eight patients reported injection-site reactions, with one treatment discontinuation. Treatment emergent anti-drug antibodies were identified in five patients but these did not affect the efficacy.

Conclusion: Alirocumab effectively and safely reduced LDL-C in these patients.

Keywords: alirocumab, PCSK9 inhibitors, familial hypercholesterolaemia, LDL-C goal, lipid-lowering therapy, cardiovascular risk, statin

Submitted 11/3/19, accepted 21/6/19
Published online 11/9/19

Cardiovasc J Afr 2019; **30**: 279–284 www.cvja.co.za

DOI: 10.5830/CVJA-2019-039

Familial hypercholesterolaemia is a genetic disorder of lipid metabolism characterised by low-density lipoprotein cholesterol (LDL-C) hypercholesterolaemia, tendon xanthomata in some but not all patients, and premature severe cardiovascular disease.[1] Founder effects are seen in multiple ethnicities in South Africa, including Afrikaners (one in 72),[2] the Ashkenazy Jewish population of Lithuanian origin (one in 67),[3] and the Indian population of Gujarati origin (more than one in 100).[4] Because heterozygous familial hypercholesterolaemia (HeFH) is characterised by severe baseline LDL-C hypercholesterolaemia, most patients are not able to reach LDL-C targets with current lipid-modifying therapies.[5]

Proprotein convertase/subtilisin kexin type 9 (PCSK9) is an important regulator of LDL-C homeostasis. It is an enzymatically inactive serine protease that is predominantly secreted by the liver. Circulating PCSK9 binds to LDL receptors on the hepatocyte surface. LDL receptors with bound PCSK9 are still internalised normally but cannot recycle to the cell surface and are degraded in the hepatocyte. Reducing the concentration of free PCSK9 reduces degradation of LDL receptors and ultimately enhances LDL-C clearance due to the increased number of LDL receptors available on the hepatocyte cell surface.[6] Alirocumab is a subcutaneously administered (SC)

Department of Medicine, Division of Lipidology and Hatter Institute for Cardiovascular Research in Africa, University of Cape Town, Cape Town, South Africa
Dirk J Blom, MB ChB, MMed (Int Med), FCP (SA), PhD, dirk.blom@uct.ac.za

Emmed Research, Pretoria West, South Africa
Johannes Breedt, MB ChB, DOH

Tread Research, Department of Cardiology, Faculty of Medicine and Health Science, University of Stellenbosch, Stellenbosch, South Africa
Lesley J Burgess, MB ChB, MMed, MSc, PGD (Int Res Ethics), PhD

Netcare Unitas Hospital, Centurion, South Africa
Iftikhar O Ebrahim, MB BCh, MMed (Int Med), Cert Cardiology (SA)

Synexus Helderberg Clinical Trial Centre, Somerset West, South Africa
Graham Ellis, BSc Hons, MB ChB, MMed (Int Med)

Clinical Research Unit, Department of Clinical Research, University of Pretoria, Pretoria, South Africa
Prashilla Soma, MB ChB, MSc (Clin Epi), PhD

Roodepoort Medicross Clinical Research Centre, Synexus Affiliated Site, Roodepoort, South Africa
Eugene van der Walt, MB ChB, MBL

Sanofi, Johannesburg, South Africa
Poobalan Naidoo, BPharm (Hons), MB BCh, MMedSc (Pharmacology)
Alet van Tonder, PhD

Carbohydrate and Lipid Metabolism Research Unit, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa
Frederick J Raal, FRCP, FCP (SA), Cert Endo, MMed (Int Med), PhD

fully human monoclonal antibody directed against PCSK9, which reduces LDL-C by up to 61%.[7]

The safety and efficacy of alirocumab in various populations have been assessed in the phase 3 ODYSSEY programme. Three of these studies investigated the effect of alirocumab in patients with HeFH and confirmed the significant reduction in LDL-C levels of alirocumab-treated patients over a period of 78 weeks.[8-10]

The ODYSSEY Open-Label Extension study (OLE; LTS13463) was a 144-week open-label extension study of alirocumab in HeFH patients who had previously participated in the ODYSSEY FH studies [replicate studies FH I (NCT01623115) and FH II (NCT01709500)], High FH (NCT01617655) or Long-Term study (NCT01507831, the HeFH stratum of patients). The objective of the ODYSSEY OLE study was to describe additional long-term safety, efficacy and tolerability of alirocumab in HeFH patients.

This report focuses specifically on the South African patients who participated in this study. Because familial hypercholesterolaemia is so common in South African founder populations, it is important to confirm that the safety and efficacy of alirocumab in South African patients are no different from that observed in the rest of the world.

Methods

The ODYSSEY OLE study was a phase 3, single-arm, open-label extension, multicentre, 144-week study evaluating the long-term safety of alirocumab when added to currently available lipid-modifying drug therapy in patients with HeFH. Detailed inclusion and exclusion criteria for these studies have been published,[8-10] and are included in Table 1. For entry into the parent study, diagnosis of HeFH could be substantiated either by genotyping or using one of the following diagnostic algorithms: Simon Broome (Scientific Steering Committee on behalf of the Simon Broome Register Group, 1991)[11] or the Dutch Lipid Network criteria with a score > 8.[12]

In FH I and FH II, patients were randomised to either alirocumab 75 mg Q2W SC or placebo. Subsequently the dose of 75 mg Q2W could be up-titrated in a blinded fashion at week 12 to 150 mg Q2W in the active-treatment arm if the LDL-C level at week 8 was > 1.8 mmol/l. In the High FH and Long-Term studies, patients were randomised to either alirocumab 150 mg Q2W or placebo. In the High FH study, the LDL-C threshold for entry was ≥ 4.14 mmol/l, whereas for Long-Term, the LDL-C threshold for entry was ≥ 1.81 mmol/l. The study flow is indicated in Fig. 1.

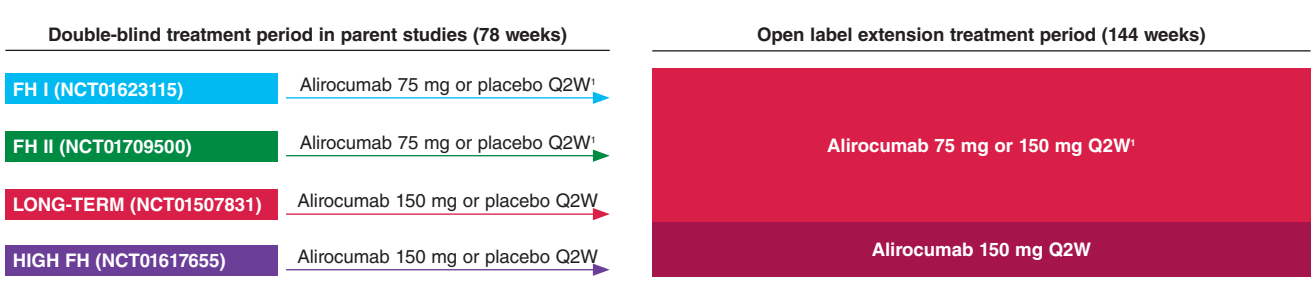
Table 1. Description of the parent studies

Variables	*ODYSSEY FH I (EFC12492)*	*ODYSSEY FH II (R727-CL-1112)*	*ODYSSEY High FH (EFC12732)*	*ODYSSEY Long-Term (LTS11717)*
Patient population enrolled	Patients diagnosed with HeFH, not adequately controlled with a maximally tolerated daily dose (MTD) of statin, stable for at least 4 weeks prior to the screening visit, with or without other lipid-modifying therapy (LMT)			
Screening LDL-C level at entry	≥ 1.80 mmol/l with a history of documented cardiovascular disease ≥ 2.59 mmol/l without a history of documented cardiovascular disease		4.14 mmol/l	2.59 mmol/l with or without documented cardiovascular disease
Sample size (HeFH patients actually randomised in the parent study)	486	249	107	385
Placebo or alirocumab dose at entry in the parent study	75 mg Q2W		150 mg Q2W	
Double-blind treatment period duration (weeks)	78			
Background LMT	MTD* statin (atorvastatin, rosuvastatin, simvastatin) ± other LMT			
% LDL-C reduction from baseline to week 24	−57.9	−51.4	−39.1	−62.0

*Maximum tolerated dose defined as:
- Rosuvastatin 20 or 40 mg daily
- Atorvastatin 40 or 80 mg daily
- Simvastatin 80 mg daily (if already on this dose for > one year)
- Patients not able to be on any of the above statin doses should be treated with the daily dose of atorvastatin, rosuvastatin or simvastatin that is considered appropriate for the patient as per the investigator's judgment or concerns. Some examples of acceptable reasons for a patient taking a lower statin dose include, but are not limited to, adverse effects on higher doses, advanced age, low body mass index, regional practices, local prescribing information, concomitant medications, co-morbid conditions such as impaired glucose tolerance or impaired fasting glucose.

The start of the OLE study corresponded with the end of the treatment visit of the double-blind treatment period for the patients enrolled in the parent studies. Upon entry into the OLE study, patients were receiving their original treatment allocation of either alirocumab 75 mg Q2W or alirocumab 150 mg Q2W, or placebo. Patients that participated in the Long-Term study had an eight-week off-treatment period before commencing the ODYSSEY OLE study.

In the ODYSSEY OLE study, patients were initiated on alirocumab 75 mg Q2W as a starting dose, regardless of the



At the start of the open-label extension study, patients were on treatment (75 or 150 mg) alirocumab Q2W or placebo
[1]Up-titration of alirocumab dose at the investigators discretion permitted at week 12 if LDL-C was ≥ 1.8 mmol/l

Fig. 1. Study flow of the ODYSSEY Open label study.

alirocumab dose during the parent studies. However, all eligible patients from High FH received a starting dose of alirocumab 150 mg Q2W because this study had selected patients with LDL-C > 4.14 mmol/l at baseline. Alirocumab was self-administered by the patient via subcutaneous injection using a pre-filled pen injector.

LDL-C levels were unblinded from week 8 to allow for dose adjustment at the investigator's discretion. Up-titration to alirocumab 150 mg Q2W could occur from week 12 onwards if LDL-C was > 1.8 mmol/l. In addition, down-titration to alirocumab 75 mg Q2W was possible at the investigator's discretion. Background treatment, including statin and other lipid-modifying treatment, were to be maintained unchanged unless tolerability warranted adjustment.

Site visits were performed at weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, 96 and 108. During these visits lipid parameters, liver function tests, creatinine phosphokinase, haematological and chemistry investigations were performed. Anti-alirocumab antibodies were assessed by the Regeneron Clinical Bioanalysis group from serum samples, as previously described.[8]

This study was conducted in accordance with the principles laid down by the 18th World Medical Assembly and all applicable amendments laid down by the World Medical Assemblies and the ICH guidelines for good clinical practice. This clinical trial was recorded in clinicaltrials.gov (NCT01954394).

Written informed consent was obtained before a patient's participation in the clinical trial and all patients were given a copy of the signed informed consent. This clinical trial protocol was approved by the relevant private and public sector ethics committee. The clinical events committee was responsible for defining, validating and classifying cardiovascular events, as well as validating the classification of the cause of all deaths.

Table 2. Baseline characteristics and medical history for ODYSSEY OLE participants in South Africa

Variables	*Placebo in parent study (n = 62)*	*Alirocumab in parent study (n = 105)*	*All (n = 167)*
Age (years), mean (SD)	55.4 (10.7)	55.6 (12.6)	55.5 (11.9)
Gender (%, male)	45.2	39.0	41.3
Race (%)			
White	85.5	87.6	86.8
Asian	1.6	0	0.6
Other	0	3.8	2.4
Black	9.7	4.8	6.6
White/Asian	3.2	3.8	3.6
Body mass index (kg/m²), mean (SD)	29.97 (6.09)	30.90 (6.40)	30.55 (6.28)
Heterozygous familial hypercholesterolaemia (%)			
Confirmation by genotyping	22.6	18.1	19.8
WHO/Simon Broome criteria	77.4	81.9	80.2
Atherosclerotic cardiovascular disease (%)	56.5	42.9	47.9
Coronary heart disease* (%)	54.8	41.9	46.7
Myocardial infarction (%)	24.2	21.0	22.2
Unstable angina (%)	16.1	9.5	12.0
Ischaemic stroke (%)	8.1	3.8	5.4
Peripheral arterial disease (%)	3.2	1.9	2.4
Coronary revascularisation procedures (%)	32.3	26.7	28.7
Hypertension (%)	58.1	47.6	51.5
Type 1 or 2 diabetes mellitus (%)	19.4	10.5	13.8
Family history of premature CHD	58.1	57.1	57.5

*According to information gathered and adverse events recorded during the parent study as well as during the pre-treatment period of the OLE study.

Statistical analysis

As this study was an open-label extension for patients from previous studies, no calculation of sample size was performed. Safety analyses were performed on the safety population, which consisted of patients receiving at least one dose or a partial dose of alirocumab in the current study. Efficacy analyses were performed on patients receiving at least one dose or a partial dose of alirocumab in the current study, with a baseline (from the parent study) LDL-C value available and with at least one LDL-C value available in the period from first alirocumab injection in the current study to last injection plus 21 days; a modified intention to treat (mITT) analysis.

Safety analysis [adverse events (including adjudicated cardiovascular events), laboratory, vital signs] was descriptive, based on the safety population. The safety analysis focused on the Treatment Emergent Adverse Events (TEAE) period defined as the time from the first dose of the current study to the last dose of alirocumab plus 70 days (10 weeks).

Efficacy variables were explored through descriptive statistics at each scheduled visit of the current study; 95% confidence intervals are provided for percent changes from baseline and success rate to reach targets.

Results

The study enrolled 167 South African patients at 14 sites. Baseline characteristics and medical history for the participants are indicated in Table 2.

All patients received treatment with lipid-modifying therapy (LMT) at study entry (Table 3). High-dose statin and ezetimibe use was 64.7 and 27.5%, respectively. Data specifying specific combinations of statins and ezetimibe used during the study were not recorded. During the OLE study, concomitant LMT was adjusted at the investigator's discretion.

Of the 42 patients for whom a change in statin therapy was reported during the OLE study, 18 reported a change in statin type, 15 reported dose adjustments in statin therapy, while nine patients discontinued statins. The reasons provided included adverse events, supply issues, treatment cost and other.

The mean (± SD) baseline LDL-C was 3.65 ± 1.9 mmol/l. Mean LDL-C level was reduced by 48.7% at week 144; mean on-treatment LDL-C was 2.30 ± 1.24 mmol/l at week 144. At week 144, 40 of 98 patients with data available (40.8%) reached target LDL-C < 1.81 mmol/l and/or ≥ 50% reduction from the parent study baseline, and 64/98 (65.3%) patients reached LDL-C < 2.59 mmol/l. During the OLE study, calculated LDL-C values < 0.65 mmol/l were reported on two consecutive occasions for four patients (Table 4, Fig. 2).

Table 3. Background lipid-modifying therapy at baseline of the ODYSSEY OLE study

Lipid-modifying therapy	*All, n (%) (n = 167)*
High-intensity statin	108 (64.7)
Atorvastatin (40 or 80 mg)	61 (36.5)
Rosuvastatin (20 or 40 mg)	45 (26.9)
Simvastatin (40 or 80 mg)	37 (22.1)
Ezetimibe	46 (27.5)
Nutraceuticals	4 (2.4)
Change in statin therapy after enrolment in OLE	42 (25.1)

Used in combination with statins or not. May include ezetimibe.

Table 4. Lipid parameters at baseline of the parent and ODYSSEY OLE studies

Lipid parameters	*Baseline at start of parent study (n = 167)*	*Baseline at the start of ODYSSEY OLE study*		
		Placebo in parent study (n = 62)	*Alirocumab in parent study (n = 105)*	*All patients included in OLE study (n = 167)*
Calculated LDL-C (mmol/l), mean (SD)	4.39 (1.56)	4.50 (1.60)	3.14 (1.96)	3.65 (1.95)
Non-HDL-C (mmol/l), mean (SD)	5.10 (1.64)	5.35 (1.68)	3.89 (2.09)	4.44 (2.07)
HDL-C (mmol/l), mean (SD)	1.24 (0.35)	1.28 (0.40)	1.32 (0.38)	1.31 (0.39)
Total cholesterol (mmol/l), mean (SD)	6.3 (1.59)	6.63 (1.60)	5.22 (2.01)	5.75 (1.98)
Fasting triglycerides (mmol/l), mean (SD)	1.53 (0.78)	1.74 (1.14)	1.56 (0.78)	1.63 (0.93)
Lipoprotein (a) (nmol/l), mean (SD)	101.75 (103.3)	106.7 (118.75)	89.5 (87)	91.5 (99.5)

A total of 76 patients (54.3%) were maintained on 75 mg Q2W for the duration of the study, while titration of alirocumab dose from 75 mg Q2W to 150 mg Q2W occurred in 64 (45.1%) patients. Down-titration to 75 mg Q2W occurred in six patients (6.6%), either due to adverse events or at the discretion of the investigator due to low LDL-C values. Compliance with alirocumab was recorded as 98.2% during the OLE study.

Nine deaths were recorded during the study: five due to cardiovascular causes (acute myocardial infarction, heart failure and other) and four due to non-cardiovascular causes (Table 5). Eight patients reported injection-site reactions with one treatment discontinuation. Treatment emergent anti-drug antibodies were identified in five patients (three persistent, two transient) but these were non-neutralising and did not affect the efficacy (Table 6).

Discussion

HeFH remains a challenging condition to manage effectively. The safety and efficacy of treatment with alirocumab in patients

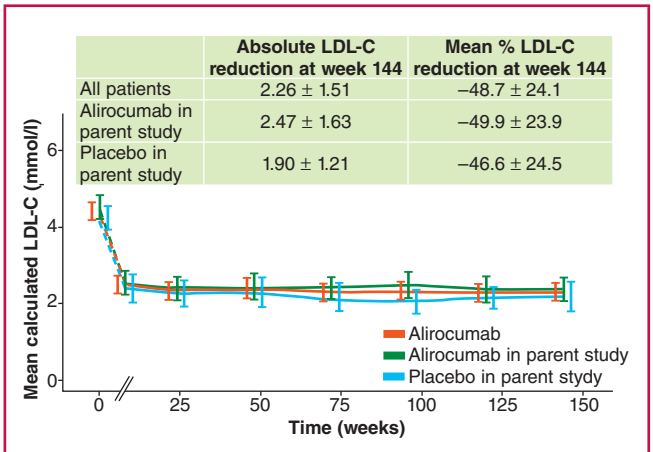


Fig. 2. Reduction in LDL-C levels observed over the 144-week study period, indicating alirocumab during the parent study, placebo during the parent study or entire ODYSSEY OLE cohort, irrespective of treatment stratification in the parent studies. Note that change in LDL-C level from the baseline of the parent study to the start of the OLE study is indicated as dotted lines based on the mITT analysis.

Table 5. Primary cause of deaths as per investigator's reports

Variables	*Placebo in parent study (n = 62)*	*Alirocumab in parent study (n = 105)*	*All (n = 167)*
Death on study, *n* (%)	4 (6.5)	5 (4.8)	9 (5.4)
Any cardiovascular event, *n* (%)	2 (3.2)	3 (2.9)	5 (3.0)
Acute myocardial infarction, *n* (%)	0	2 (1.9)	2 (1.2)
Heart failure or cardiogenic shock, *n* (%)	1 (1.6)	1 (1.0)	2 (1.2)
Other cardiovascular causes, *n* (%)	1 (1.6)	0	1 (0.6)
Non-cardiovascular event, *n* (%)	2 (3.2)	2 (1.9)	4 (2.4)

with HeFH have been reported in previous phase 3 studies.[8-10] However, while these studies were conducted over a period of 78 weeks, the long-term safety of treatment with alirocumab in this patient population had not previously been investigated. The ODYSSEY OLE study provides data on a further 144 weeks of treatment with open-label alirocumab.

The South African arm of the ODYSSEY OLE study confirmed the safety, tolerability and sustained, persistent, long-term reduction of LDL-C levels in South African patients with HeFH. The LDL-C reduction observed in the South African arm of the OLE study at week 144 was 48.7%, mimicking the reported LDL-C reduction in the parent studies as well as the LDL-C reduction observed in the global OLE study (47.9% at week 96).[13]

The global ODYSSEY OLE study enrolled a total of 985 patients diagnosed with HeFH. At baseline, 977 (99.2%) patients were on treatment with statins, while 571 (58.0%) patients

Table 6. Adverse events and safety laboratory values (safety population)

Adverse event	*Placebo in parent study n (%) (n = 62)*	*Alirocumab in parent study n (%) (n = 105)*	*All, n (%) (n = 167)*
Treatment-emergent adverse events (TEAE)	58 (93.5)	98 (93.3)	156 (93.4)
Treatment-emergent serious adverse events	29 (46.8)	30 (28.6)	59 (35.5)
TEAEs leading to death	4 (6.5)	5 (4.8)	9 (5.4)
TEAEs leading to permanent discontinuation	5 (8.1)	9 (8.6)	14 (8.4)
Death	4 (6.5)	5 (4.8)	9 (5.4)
TEAEs occurring in ≥ 5% in either group			
Gastroenteritis	5 (8.1)	12 (11.4)	17 (10.2)
Dental and oral soft tissue infections	4 (6.5)	8 (7.6)	12 (7.2)
Tooth abscess	3 (4.8)	8 (7.6)	11 (6.6)
Bronchitis	6 (9.7)	10 (9.5)	16 (9.6)
Upper respiratory tract infection	8 (12.9)	21 (20.0)	29 (17.4)
Urinary tract infection	9 (14.5)	7 (6.7)	16 (9.6)
Influenza	9 (14.5)	15 (14.3)	24 (14.4)
Viral upper respiratory tract infection	5 (8.1)	9 (8.6)	14 (8.4)
Headache	2 (3.2)	7 (6.7)	9 (5.4)
Angina pectoris	4 (6.5)	4 (3.8)	8 (4.8)
Hypertension	6 (9.7)	5 (4.8)	11 (6.6)
Hiatus hernia	4 (6.5)	1 (1.0)	5 (3.0)
Gastritis	4 (6.5)	6 (5.7)	10 (6.0)
Diarrhoea	2 (3.2)	6 (5.7)	8 (4.8)
Arthralgia	6 (9.7)	10 (9.5)	16 (9.6)
Osteoarthritis	5 (8.1)	4 (3.8)	9 (5.4)
Muscle spasms	3 (4.8)	6 (5.7)	9 (5.4)
Back pain	2 (3.2)	6 (5.7)	8 (4.8)
Pain in extremity	1 (1.6)	7 (6.7)	8 (4.8)
Injection-site reaction	2 (3.2)	6 (5.7)	8 (4.8)
Fatigue	4 (6.5)	1 (1.0)	5 (3.0)
Influenza-like illness	2 (3.2)	7 (6.7)	9 (5.4)

received ezetimibe treatment.[13] In the South African cohort, statin treatment was reported by 143 (85.6%) and ezetimibe treatment by 46 (27.5%) patients. It is not clear how many patients were on combination LMT.

Higher reductions in LDL-C would have been expected if more participants were up-titrated to the maximum dose of alirocumab. A total of 76 patients (54% of the SA cohort) remained on treatment with 75 mg of alirocumab Q2W for the duration of the study, even though up-titration of the dose was allowed at the investigator's discretion.

A greater LDL-C reduction of 61% was reported in the ODYSSEY Long-Term study at week 24.[9] However, all the participants in the active arm of the ODYSSEY Long-Term study received the maximum dose of alirocumab (150 mg every two weeks), as opposed to only 46% of participants receiving the maximum dose of alirocumab in ODYSSEY OLE.

In South Africa the diagnosis of HeFH is based mainly on clinical criteria as per the Simon Broome criteria.[11] or the Dutch Lipid Network criteria with a score > 8.[12] Genetic testing is rarely performed due to cost.

According to the 2017 European Society of Cardiology/ European Atherosclerosis Society guidelines for the use of PCKS9i, HeFH patients should be considered for treatment with PCSK9i in two scenarios: patients on treatment with maximum tolerated doses of statins and/or ezetimibe where LDL-C remains > 4.5 mmol/l, or where additional risk factors are present and LDL-C remains > 3.6 mmol/l.[14]

In the present study, treatment-emergent anti-drug antibodies were identified in five patients during the study but were reported to be non-neutralising. Indeed, sustained LDL-C reduction was observed in all patients over the 144-week study period.

Drug-neutralising anti-drug antibodies were induced by treatment with bococizumab, a humanised antibody containing approximately 3% murine sequence, resulting in attenuated LDL-C reduction.[15] Alirocumab is, however, a fully humanised PCSK9 inhibitor. A review of 10 alirocumab studies has shown that while anti-drug antibodies were observed in approximately 5.1% of patients receiving the active treatment, LDL-C reduction was not attenuated.[16]

Additional adverse effects observed in the study were comparable to those reported in previous studies with alirocumab,[8-10,13] and included injection-site reactions and athralgia. The safety results must be interpreted with caution as the sample size was relatively small, and rare adverse events may not have been detected. Nevertheless, the safety profile of alirocumab, especially related to muscle symptoms, was favourable. This is especially relevant give that statin-associated muscle symptoms and statin intolerance may limit adherence to statins.[17]

An advantage of the ODYSSEY OLE study is that the data collected partially represent real-world evidence of the safety and efficacy of alirocumab: during the study alirocumab was self-administered by patients, LMT and alirocumab doses were adjusted at the investigator's discretion, and study visits were fewer than in previous studies in the ODYSSEY programme.

Conclusion

Results from the South African cohort enrolled in the ODYSSEY OLE study confirm that alirocumab was safe, efficacious and well tolerated in the South African HeFH patients.

All authors were investigators in the study. Sanofi was the sponsor of the study. AvT and PN are employees of Sanofi. Neither AvT nor PN owns stocks in Sanofi. DB has received clinical trial fees, and honoraria for advisory board participation and for speaking from Sanofi. FR has received research grants, honoraria or consulting fees for professional input and/or delivered lectures from Sanofi, Regeneron, Amgen and The Medicines Company.

References

1. Nordestgaard BG, Chapman MJ, Humphries SE, *et al*. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European atherosclerosis society. *Eur Heart J* 2013; **34**: 3478–3390.
2. Steyn K, Goldberg YP, Kotze MJ, Steyn M, Swanepoel AS, Fourie JM, *et al*. Estimation of the prevalence of familial hypercholesterolaemia in a rural Afrikaner community by direct screening for three Afrikaner founder low-density lipoprotein receptor gene mutations. *Hum Genet* 1996; **98**(4): 479–484.
3. Reich DE, Lander ES. On the allelic spectrum of human disease. *Trends Genet* 2001; **17**(9): 502–510.
4. Rubinsztein DC, van der Westhuyzen DR, Coetzee GA. Monogenic primary hypercholesterolaemia in South Africa. *S Afr Med J* 1994: **84**(6); 339–344.
5. Hopkins PN, Stephenson S, Wu LL, Riley WA, Xin Y, Hunt SC. Evaluation of coronary risk factors in patients with heterozygous familial hypercholesterolemia. *Am J Cardiol* 2001; **87**(5): 547–553.
6. Della Pepa G, Bozzetto L, Annuzzi G, Rivellese AA. Alirocumab for the treatment of hypercholesterolaemia. *Expert Rev Clin Phar* 2017; **10**(6): 571–582.
7. Vally M, Kathrada F, Butkow N. An update on the measurement and management of cholesterol with specific reference to secondary prevention of cardiovascular disease (CVD). *S Afr Fam Pract* 2018; **60**(1): 15–20.
8. Kastelein JJ, Ginsberg HN, Langslet G, Hovingh GK, Ceska R, Dufour R, *et al*. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. *Eur Heart J* 2015; **36**(43): 2996–3003.
9. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, *et al*. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015; **372**(16): 1489–1499.
10. Ginsberg HN, Rader DJ, Raal FJ, Guyton JR, Baccara-Dinet MT, Lorenzato C, *et al*. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia and LDL of 160 mg/dl or higher. *Cardiovasc Drugs Ther* 2016; **30**(5): 473–483.
11. Simon Broome Register Group. Risk of fatal coronary heart disease in familial hypercholesterolaemia. *Br Med J* 1991; 893–896.
12. Defesche JC, Lansberg PJ, Umans-Eckenhausen MA, Kastelein JJ. Advanced method for the identification of patients with inherited hypercholesterolemia. *Semin Vasc Med* 2004; **4**: 59–65.
13. Farnier M, Hovingh GK, Langslet G, Dufour R, Baccara-Dinet MT, Din-Bell C, *et al*. Long-term safety and efficacy of alirocumab in patients with heterozygous familial hypercholesterolemia: An open-label extension of the ODYSSEY program. Atherosclerosis 2018; ODYSSEY program. *Atherosclerosis* 2018; **278**: 307–314.
14. Landmesser U, Chapman MJ, Stock JK, Amarenco P, Belch JJ, Borén J, *et al*. 2017 update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia. *Eur Heart J* 2017; **39**(14): 1131–1143.

15. Ridker PM, Tardif JC, Amarenco P, Duggan W, Glynn RJ, Jukema JW, *et al*. Lipid-reduction variability and antidrug-antibody formation with bococizumab. *N Engl J Med* 2017; **376**(16): 1517–1526.
16. Roth EM, Goldberg AC, Catapano AL, Torri A, Yancopoulos GD, Stahl N, *et al*. Antidrug antibodies in patients treated with alirocumab. *N Engl J Med* 2017; **376**(16): 1589–1590.
17. Lansberg P, Lee A, Lee ZV, Subramaniam K, Setia S. Nonadherence to statins: individualized intervention strategies outside the pill box. *Vasc Health Risk Manag* 2018; **14**: 91–102.

Inflammation, the possible link between heart disease and depression

People with heart disease are more likely to suffer from depression, and the opposite is also true. Now, scientists at the University of Cambridge believe they have identified a link between these two conditions: inflammation – the body's response to negative environmental factors, such as stress.

While inflammation is a natural response necessary to fight off infection, chronic inflammation, which may result from psychological stress as well as lifestyle factors such as smoking, excessive alcohol intake, physical inactivity and obesity, is harmful.

The link between heart disease and depression is well documented. People who have a heart attack are at a significantly higher risk of experiencing depression. Yet scientists have been unable to determine whether this is due to the two conditions sharing common genetic factors or whether shared environmental factors provide the link.

'It is possible that heart disease and depression share common underlying biological mechanisms, which manifest as two different conditions in two different organs, the cardiovascular system and the brain,' says Dr Golam Khandaker, a Wellcome Trust intermediate clinical fellow at the University of Cambridge. 'Our work suggests that inflammation could be a shared mechanism for these conditions.'

Khandaker and colleague Dr Stephen Burgess led a team of researchers from Cambridge who examined this link by studying data relating to almost 370 000 middle-aged participants of UK Biobank. First, the team looked at whether family history of coronary heart disease was associated with risk of major depression. They found that people who reported at least one parent having died of heart disease were 20% more likely to develop depression at some point in their life.

Next, the researchers calculated a genetic risk score for coronary heart disease, a measure of the contribution made by the various genes known to increase the risk of heart disease. Heart disease is a so-called 'polygenic' disease – in other words, it is caused not by a single genetic variant, but rather by a large number of genes, each increasing an individual's chances of developing heart disease by a small amount. Unlike for family history, however, the researchers found no strong association between the genetic predisposition for heart disease and the likelihood of experiencing depression.

Together, these results suggest that the link between heart disease and depression cannot be explained by a common genetic predisposition to the two diseases. Instead, it implies that something about an individual's environment, such as the risk factors he/she is exposed to, not only increases the risk of heart disease, but at the same time increases the risk of depression.

This finding was given further support by the next stage of the team's research. They used a technique known as Mendelian randomisation to investigate 15 biomarkers – biological 'red flags' – associated with increased risk of coronary heart disease. Mendelian randomisation is a statistical technique that allows researchers to rule out the influence of factors that otherwise confuse, or confound, a study, such as social status. Of these common biomarkers, they found that triglycerides and the inflammation-related proteins interleukin-6 (IL-6) and C-reactive protein (CRP) were also risk factors for depression.

Both IL-6 and CRP are inflammatory markers that are produced in response to damaging stimuli, such as infection, stress or smoking. Studies by Khandaker and others have previously shown that people with elevated levels of IL-6 and CRP in the blood are more prone to develop depression, and that levels of these biomarkers are high in some patients during acute depressive episodes. Elevated markers of inflammation are also seen in people with treatment-resistant depression. This has raised the prospect that anti-inflammatory drugs might be used to treat some patients with depression.

Khandaker is currently involved in a clinical trial to test tocilizumab, an anti-inflammatory drug used for the treatment of rheumatoid arthritis that inhibits IL-6, to see if reducing inflammation leads to improvement in mood and cognitive function in patients with depression.

While the link between triglycerides and coronary heart disease is well documented, it is not clear why they, too, should contribute to depression. The link is unlikely to be related to obesity, for example, as this study has found no evidence for a causal link between body mass index and depression.

'Although we don't know what the shared mechanisms between these diseases are, we now have clues to work with that point towards the involvement of the immune system,' says Burgess. 'Identifying genetic variants that regulate modifiable risk factors helps to find what is actually driving disease risk.'

Dr Sophie Dix, director of research at MQ, says: 'This study adds important new insight into the emergence and risk of depression, a significantly under-researched area. Taking a holistic view of a person's health, such as looking at heart disease and depression together, enables us to understand how factors like traumatic experiences and the environment impact on both our physical and mental health.

'This research shows clearly the shared biological changes that are involved. This not only opens opportunities for earlier diagnosis, but also creates a solid foundation for exploring new treatments or using existing treatments differently. We need to stop thinking about mental and physical health in isolation and continue this example of bringing sciences together to create real change.'

Source: Medical Brief 2019