

Familial hypercholesterolaemia in children

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Abstract

Familial hypercholesterolaemia (FH) affects about one in 500 in the UK population. There are no symptoms or signs of raised cholesterol in children and so individuals can only be identified by screening, usually as a 'cascade' from known probands. Once identified, such children should be treated to prevent premature atherosclerosis.

Key words: familial hypercholesterolaemia, children, genetic testing, statins.

Br J Cardiol 2006;**13**:191–4

Introduction

Familial hypercholesterolaemia (FH) is probably the commonest single gene disorder, with an assumed prevalence in the UK population of about one in 500. This means that the average secondary school probably has three or four pupils with FH. Compared with FH, the other lipid disorders found in childhood (table 1) are all very rare.

The clinical diagnosis of FH is confirmed by the clustering of high cholesterol levels (> 7.5 mmol/l) in first- or second-degree relatives and the presence of tendon xanthomata (TX; figure 1) in at least one member of the family.^{1,2} Alternatively, identification of a functional genetic defect can be used.³

Without effective treatment, FH males aged 20 to 40 years are 100 times more likely to develop coronary artery disease than unaffected normals,¹ compared with a risk ratio of three to six for diabetes⁴ and two to three for cigarette smoking.⁵ Clearly the identification and treatment of FH at a younger age would be of benefit, but random screening of the population would not be cost-effective. Cascade targeted screening from known affected individuals has been recommended in the 2003 White Paper *Our Inheritance, Our Future*. It is likely that increasing numbers of children will be found to be affected, and this raises management and treatment issues.

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Table 1. Lipid disorders in childhood

Atherogenic

- Familial hypercholesterolaemia
- Familial combined hyperlipidaemia
- Remnant (type III) hyperlipidaemia
- Apolipoprotein A1-CIII deficiency
- Lecithin:cholesterol acyl transferase (LCAT) deficiency
- Hyperapobetalipoproteinaemia

Non-atherogenic

- Tangier disease
- Fish-eye disease
- Lipoprotein lipase deficiency
- Apolipoprotein CII deficiency

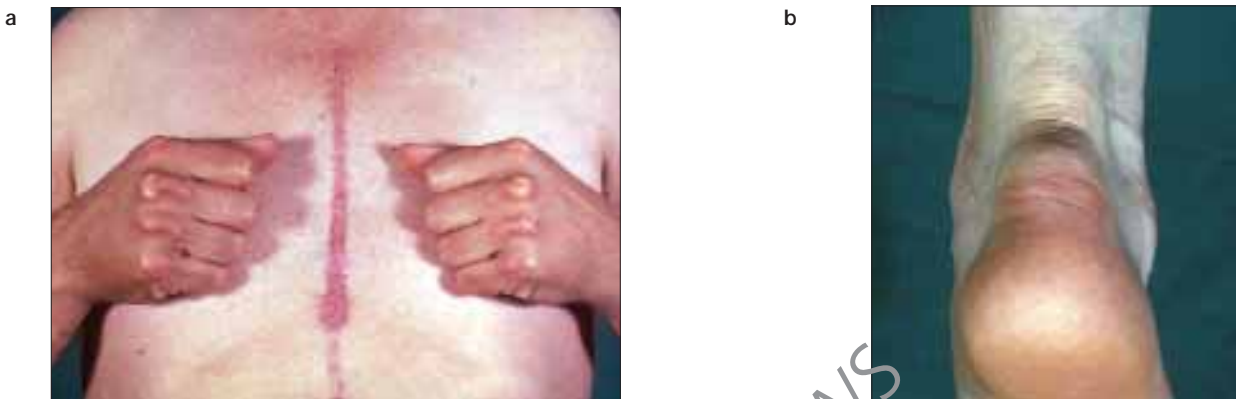
Possibly protective against atherosclerosis

- A- or hypobetalipoproteinaemia
- Hyperalphalipoproteinaemia

Genetics of FH

FH is inherited as an autosomal co-dominant disorder, which means that the sex distribution is equal. Affected individuals inherit a defective allele from one parent (i.e. heterozygous FH [HEFH]) and will pass on the defective gene to one in two of their offspring. Unaffected individuals cannot pass it on and the disorder cannot 'skip' a generation. In certain populations of the

Figure 1. **a:** shows tendon xanthomata and a coronary artery bypass grafting scar in an adult with heterozygous familial hypercholesterolaemia due to an intron splicing defect in the LDLR gene, c.1845+11c>g;³ **b:** shows Achilles tendon thickening in the same patient. Note that in children, these signs are only observed in homozygous familial hypercholesterolaemia



world in whom the gene pool is more restricted, such as Afrikaansers, French Canadians and Lebanese, the prevalence of FH is much greater, up to one in 50 of the population being affected. In the majority of cases, the fault lies in the gene encoding for the low-density lipoprotein receptor (LDLR) which is responsible for the catabolism of ApoB-containing particles.⁶ With only half the normal number of functioning LDLRs available, circulating plasma cholesterol levels are approximately doubled and there is a marked predisposition to premature coronary artery disease.

The gene encoding the LDLR is on chromosome 19p.13.2, and nearly 800 mutations have been described (<http://www.ucl.ac.uk/fh>; <http://www.umd.necker.fr>). The precise defect varies but can be identified in 70–90% of FH families.³ In about 10% of families, the problem is a missense mutation in the ligand for the LDLR, ApoB (R3500Q).⁷ In some families, no genetic abnormality can be defined, despite the presence of tendon xanthomata (TX) in the family.³

Homozygous FH

In theory, if an individual with HeFH meets by chance another individual with HeFH, then one in four of their offspring would have homozygous FH (HoFH). This would give a prevalence of one in 500 x 500 x 4 in the population, i.e. 1 in 10⁶. In practice, HoFH is much rarer than this in the UK and there are currently no individuals with HoFH in Ireland (population > 5 million). In other areas with restricted gene pools, such as Lebanese Christians in whom first-cousin marriages are common, HoFH becomes a real possibility.⁸

HoFH is a serious disease, with a virtual absence of functioning LDLRs, cholesterol levels of > 20 mmol/L, premature atherosclerosis, TX in childhood, and death in the second or third decade if untreated. Drug treatment is unsatisfactory except for

the cholesterol absorption inhibitor ezetimibe,⁹ and LDL-apheresis is the mainstay of treatment.¹⁰ Liver transplantation has been used to donate LDLRs,¹¹ and direct injection into the portal vein of LDLR-encoded recombinant retroviruses has also been performed.¹²

Diagnosis of FH in childhood

In children with HeFH, there are no symptoms or signs, and so the diagnosis can only be made by blood testing. Although normal ranges for total and LDL-cholesterol in children have been published,¹³ there is considerable variability and hence overlap between affected and unaffected individuals.¹⁴ Genotyping is much more satisfactory, when the LDLR defect for the family has been characterised, but the test is not as yet widely available. This may change in the near future with the increasing availability of 'chip' technology.

Individual children with HeFH are exposed to inappropriately high cholesterol levels from birth or before but, in practice, treatment is rarely possible before school age. At that stage, when a child is aged four to five, it is very helpful to know whether he/she is affected as there is an opportunity to teach healthy eating (see below). Alternatively, knowing that the child is not affected can be very reassuring. Research has shown that there are no negative psychological features associated with this knowledge, either in the child or the parents.¹⁵

Treatment of FH in children

Treatment of HeFH in childhood is recommended because the adverse long-term effects of severe hypercholesterolaemia have been well described.¹ In addition, there is direct evidence that there is endothelial dysfunction in young people with HeFH,¹⁶ which is reversible,¹⁷ and evidence of carotid artery damage,¹⁸ and so the process of atherosclerosis has already started. The

treatment of affected children should be supervised by a lipid clinic in view of the complex issues involved.¹⁹

As with adults, initial advice is on diet but this can be problematic in childhood, not least because of school meals! Very low fat or low cholesterol diets are inappropriate and potentially harmful. The best that can be achieved in terms of cholesterol reduction with a 'healthy diet' is about 15%, and this is not enough to normalise levels in patients with FH. Nevertheless, this is a good time to teach children the principles of a healthy diet, with more emphasis on cereals and fruit, and viewing fries, sweets, crisps and so on as occasional treats rather than the mainstay of their diet.

A recent study from the Simon Broome Association²⁰ identified male sex and cigarette smoking as the two most important factors in determining prognosis in patients with HeFH. Affected children should be left in no doubt that it is imperative that they *never* start smoking, whatever the peer pressures to do so. Apart from this, though, they should regard themselves as being normal in every way. HeFH, particularly if well treated, is no bar to any sport, no matter how intense – most of the sudden deaths on sports fields are due to cardiomyopathy rather than premature coronary artery disease.²¹

There remains controversy on when to initiate drug treatment. It is important to consider all the variables before making such a decision. In particular, if there is a very strong history of premature coronary artery disease in the family, then it is reasonable to start treatment early, as soon as dietary intervention has been given a chance. If, on the other hand, the family history is relatively benign then drug treatment can be deferred until later.

Resins were used in children in the past, but they are unpalatable in the quantity required to effect a significant cholesterol reduction, and are now outmoded. Fenofibrate in the low-dose preparation (Lipantil Micro 67*) is licensed for use in children but is only moderately effective. The most effective drugs by far are the statins. Studies in children have confirmed effective cholesterol reduction without any observed effects on growth or development.²²⁻²⁶ In the UK, pravastatin is licensed for use in children with HeFH from the age of eight years at the reduced dose of 10–20 mg daily, and from 14 years at 40–40 mg. Atorvastatin is licensed from ages 10–17 years at the 10–20 mg dose. Other statins are not yet licensed for use in children with HeFH. Girls should be told not to conceive whilst on a statin. The cholesterol absorption inhibitor ezetimibe is not recommended for children under 10 years, unless they have HoFH.⁹

Conclusions

HeFH should be actively sought and treated in children. As it is thought that the main risk in HeFH derives from the inappropriate elevations of LDL cholesterol, and children have been exposed to such increases from or before birth, then it is hoped that early aggressive treatment will prevent the development of premature atherosclerosis. If cholesterol levels are normalised, then there is no reason why the individual should be barred from active jobs or sports, and no reason why they should not be



Key messages

- Familial hypercholesterolaemia (FH) affects about one in 500 of the UK population
- Affected children have evidence of premature atherosclerosis
- Affected children should be identified and treated
- The cardiovascular risk of FH can be reduced by effective treatment

accepted for life insurance at standard rates. By an active screening policy the threat of FH could be greatly reduced.

Conflict of interest

None declared.

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Tracleer Abbreviated Prescribing Information
(Please refer to the full SmPC before prescribing)



Tracleer 62.5 mg and 125mg film-coated tablets

Uses Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with grade III functional status. Efficacy has been shown in Primary PAH & PAH secondary to scleroderma without significant interstitial pulmonary disease. **Dosage and administration** Treatment should only be initiated and monitored by a physician experienced in the treatment of pulmonary arterial hypertension. Treatment should be initiated at a dose of 62.5mg twice daily for 4 weeks and then increased to the maintenance dose of 125mg twice daily. Tablets are to be taken orally morning and evening, with or without food. In the case of clinical deterioration (e.g., decrease in 6-minute walk test distance by at least 10% compared with pre-treatment measurement) despite Tracleer treatment for at least 8 weeks (target dose for at least 4 weeks), alternative therapies should be considered. However, some patients who show no response after 8 weeks of treatment with Tracleer may respond favourably after an additional 4 to 8 weeks of treatment. If the decision to withdraw Tracleer is taken, it should be done gradually while an alternative therapy is introduced. Patients not responding well to 125mg twice daily of Tracleer may slightly improve their exercise capacity when the dose is increased to 250mg twice daily. A careful risk/benefit assessment should be made, taking into consideration that the liver toxicity is dose dependent. **Dosage in hepatic impairment** Mild: No dose adjustment required. Moderate/Severe: Contraindicated. **Dosage in renal impairment** No dose adjustment required. No dose adjustment is required in patients undergoing dialysis. **Dosage in elderly patients** No dose adjustment required. **Children** Safety and efficacy in patients under the age of 12 years have not been substantially documented although the following dose regimen has been used in a clinical study: Body weight (kg) / initiation dose (4 weeks) / Maintenance dose: 10kg <= 20kg / 31.25mg OD / 31.25mg BD; 20kg <= 40kg / 31.25mg BD / 62.5mg BD; <40kg / 62.5mg BD / 125mg BD. No data are available in children under 3 years. **Contraindications** Hypersensitivity to Tracleer or any of the excipients, moderate to severe hepatic impairment, baseline values of liver aminotransferases (AST and/or ALT), greater than 3 times the upper limit of normal, concomitant use of cyclosporine A, pregnancy, women of childbearing potential who are not using a reliable (barrier) method of contraception (see later). **Special warnings and special precautions** The efficacy of Tracleer has not been established in patients with severe pulmonary arterial hypertension. Transfer to a therapy that is recommended at the severe stage of the disease (e.g., epoprostenol) should be considered if the clinical condition deteriorates. The benefit/risk balance of Tracleer has not been established in patients with WHO class I or II functional status of PAH. No studies have been performed in secondary PAH other than related to connective tissue diseases (primarily scleroderma). Tracleer should only be initiated if the systemic systolic blood pressure is higher than 85 mmHg.

Liver function Elevations in liver aminotransferases, i.e., aspartate and alanine aminotransferases (AST and/or ALT), associated with Tracleer are dose dependent. Liver enzyme changes typically occur within the first 16 weeks of treatment. Recommendations are as follows:

- Liver aminotransferase levels must be measured prior to initiation of treatment and subsequently at monthly intervals.
- Liver aminotransferase levels must be measured 2 weeks after any dose increase.
- In the event of a rise in liver aminotransferase levels within pre-treatment values. The advice of a hepatologist is recommended. AST/ALT levels must then be checked within 3 days after re-introduction, then again after 2 weeks, and thereafter according to the recommendations above.
- In case of associated clinical symptoms of liver injury, or a >8 ULN rise in liver aminotransferases, treatment must be stopped and re-introduction of Tracleer is not to be considered.

Haemoglobin concentration Tracleer was associated with a dose-related, modest decrease in haemoglobin concentration but decreases are not progressive, and stabilise after the first 4 – 12 weeks of treatment. It is recommended that haemoglobin concentrations be checked prior to initiation of treatment, monthly for the first 4 months, and quarterly thereafter. Use in women of childbearing potential Not to be initiated in women of childbearing potential unless they practise reliable contraception and have a negative pre-treatment pregnancy test. Monthly pregnancy tests during are recommended. **Pulmonary veno-occlusive disease (PVOD)** Cases of life threatening pulmonary oedema have been reported with vasodilators (mainly prostacyclin) when used in those patients. Should signs of pulmonary oedema occur in PAH patients, the possibility of associated veno-occlusive disease should be considered. There have been rare reports of pulmonary oedema in patients treated with Tracleer who had a suspected diagnosis of PVOD. PAH patients with concomitant left ventricular failure No specific study has been performed. It is recommended that patients be monitored for signs of fluid retention. Should this occur, treatment with diuretics is recommended, or the dose of existing diuretics should be increased. Treatment with diuretics should be considered in patients with evidence of fluid retention before the start of treatment with Tracleer. Glibenclamide Not recommended, due to an increased risk of elevated liver aminotransferases. Fluconazole Not recommended. Concomitant administration of both a CYP3A4 inhibitor and a CYP2C9 inhibitor should be avoided. **Pregnancy and lactation** Tracleer is contraindicated in pregnancy, and must be considered a human teratogen. Tracleer may render hormonal contraceptives ineffective. Women of childbearing potential must use a reliable alternate method of contraception during, and for 3 months after, treatment. Monthly pregnancy tests during treatment are recommended. **Use during lactation** Not recommended. **Ability to drive and use machines** Tracleer may cause dizziness, which could influence the ability to drive or use machines. **Side effects** **All Placebo Controlled Trials** In eight placebo-controlled studies, 6 of which were for indications other than PAH, a total of 677 patients were treated with Tracleer at daily doses ranging from 100mg to 2000mg and 288 patients were treated with placebo. The foreseen treatment duration ranged from 2 weeks to 6 months. The adverse drug reactions that occurred more frequently with Tracleer than with placebo (in >=3% of Tracleer-treated patients, with >=2% difference) were headache (15.8% vs. 12.8%), flushing (6.6% vs. 1.7%), abnormal hepatic function (5.9% vs. 2.1%), led oedema (4.7% vs. 1.4%), and anaemia (3.4% vs. 1.0%), all of which were dose related. **Placebo Controlled trials in PAH** At a Tracleer dose of 125 or 250mg BD the following adverse drug reactions that occurred in >=3% of patients, and more frequently in patients on Tracleer, were:

Adverse event	Placebo (n=80) No.	%	Tracleer (n=165) No.	%
Upper respiratory tract infection	9	11	20	12
Nasopharyngitis	6	8	18	11
Pneumonia	1	1	5	3
Oedema lower limb	4	5	13	8
Palpitations	1	1	8	5
Oedema	2	3	7	4
Dyspepsia	0	0	7	4
Dry Mouth	1	1	5	3
Headache	16	20	36	22
Flushing	4	5	15	9
Hypotension	3	4	11	7
Pruritus	0	0	6	4
Fatigue	1	1	6	4
Hepatic Function Abnormal	2	3	14	8

Treatment discontinuations due to adverse events were less frequent in Tracleer- than placebo treated patients. **Post-marketing experience** Based on exposure of about 13,000 patients to Tracleer, the majority of adverse events have been similar to those reported in clinical trials. Common events seen included nausea; uncommon events included vomiting, abdominal pain, diarrhoea, aminotransferase elevations associated with hepatitis and/or jaundice, hypersensitivity reactions including dermatitis, pruritus and rash; rare events included anaphylaxis and/or angioedema. **Laboratory abnormalities** **Liver test abnormalities** In studies in patients with PAH, the incidence of elevated liver aminotransferases (>3 x ULN) was 12.7% in Tracleer-treated patients (N = 165), 11.6% in patients treated with 125mg BD and 14.3% in patients treated with 250mg BD. Eight-fold increases were seen in 2.1% of PAH patients on 125mg BD and 7.1% of PAH patients on 250mg BD. **Haemoglobin** The mean decrease in haemoglobin concentration from baseline to trial completion for the Tracleer- and placebo-treated patients was 0.9 g/dl and 0.1 g/dl respectively. **Overdose** Massive overdose may result in pronounced hypotension requiring active cardiovascular support. **Packaging Quantity and Price** Tracleer 62.5 mg 56 film-coated tablets £1541.00 UK, €2,538.00 Ireland or Tracleer 125 mg 56 film coated tablets £1541.00 UK, €2,538.00 Ireland in aluminium blisters (all ex VAT). **Marketing Authorisation Holder and Numbers** Actelion Registration Ltd BSI Building 13th Floor 389 Chiswick High Road London W4 4AL UK EU/1/02/220/001/2/3/4/5. **Legal Category** POM. **Date of PI Preparation** 4 January 2006. Medical Information TEL UK 0845 0750555; TEL Ireland 01890 771648.

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