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Original Research Article

Fenofibrate in the management of AbdoMinal aortic anEurysm (FAME)-2: the study protocol for a multi-centre, randomised, placebo-controlled trial

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ABSTRACT

Background: Abdominal aortic aneurysms (AAAs) are a leading cause of mortality worldwide but have no recognised medical therapy. Pre-clinical studies indicate that osteopontin plays an important role in the pathogenesis of AAA via a number of mechanisms. This trial aims to assess the potential of fenofibrate to favourably alter biomarkers associated with AAA pathology.
Methods: Fenofibrate in the management of AbdoMinal aortic anEurysm (FAME)-2 is a multi-centre, prospective, randomised, double-blind, placebo-controlled clinical trial to assess the effect of 24 weeks of oral therapy with 145 mg of fenofibrate on key pathological markers of AAA. A total of 140 participants with an AAA measuring between 35-49 mm will be randomly assigned to either 145 mg of fenofibrate once per day or identical placebo for a period of 24 weeks. Primary outcome measures will be serum concentrations of osteopontin and kallistatin. Secondary outcome measures will include serum levels of resistin, lipids, matrix metalloproteinases and pro-inflammatory cytokines, circulating concentrations of AAA biomarkers, and AAA diameter as assessed by ultrasound.
Conclusions: This study represents the next step in the assessment of a potential novel medical therapy for AAA.

Keywords: Abdominal aortic aneurysm, Fenofibrate, Clinical trial, Osteopontin, Kallistatin

INTRODUCTION

An abdominal aortic aneurysm (AAA) is a permanent dilatation of the infrarenal aorta that can lead to death as a result of aortic rupture.[1,2] AAAs are present in ~5% of men and ~1% of women aged over 65 years, but have no known medical therapy.[3-7] Current guidelines comprise regular ultrasound imaging until a diameter threshold is reached (typically 55 mm), at which point surgical intervention is considered.[8] Patients with symptomatic or rapidly expanding AAAs (>10 mm/year) should also be

considered for surgical repair. However, currently there are no treatments for small AAAs or AAAs in patients not suitable for surgical repair.

Pre-clinical studies employing rodent models of AAA have revealed that the peroxisome proliferator activator alpha (PPARα) ligand fenofibrate reduces AAA development.[9,10] Data from one study suggests this effect may be due to a concomitant reduction of the pro-inflammatory protein osteopontin (OPN), and reduced recruitment of macrophages to the aortic wall.[9] OPN deficiency has been reported to protect against AAA formation in a mouse model, and in humans, serum OPN levels have been shown to be associated with AAA presence and growth.[11,12] One likely mechanism underlying this association is the ability of OPN to promote macrophage accumulation within the aorta, resulting in the production of a range of proteolytic enzymes, such as matrix metalloproteinases (MMPs), which are known to cause aortic destruction.[11,13,14] Additional studies in rodent models indicate that fenofibrate downregulates OPN expression in hypertrophied left ventricle cells and dysfunctional renal cells, whilst a short course of bezafibrate reduced circulating concentrations of OPN by ~23% in diabetic patients.[15-17] The observed ability of fenofibrate to downregulate OPN, potentially reducing macrophage infiltration and associated release of proteolytic enzymes represents a novel approach to limit AAA progression.

Fenofibrate has other reported effects that suggest it may limit aortic destruction. Previous studies have indicated that short-term fenofibrate therapy reduces low density lipoprotein (LDL) and triglyceride serum concentrations, and increases high density lipoprotein (HDL) serum concentrations.[18-20] Low circulating concentrations of HDL and high circulating concentrations of triglyceride have been associated with AAA in patients.[21-23] Obesity and visceral fat accumulation are risk factors for AAA, with analysis suggesting circulating adipokines, in particular resistin, may be the cause.[24] Previous studies have reported that fenofibrate downregulates resistin production from visceral adipose tissue, thus providing a further potential mechanism by which fenofibrate could stabilise AAAs.[25,26] A large body of data implicates MMPs in AAA.[21,27] MMPs, including MMP-9, activate pro-inflammatory cytokines and have been shown to cleave OPN to a more active form.[28,29] Data from in vitro studies suggests that fenofibrate inhibits MMP-9 production by vascular cells such as macrophages and endothelial cells.[30-32] Thus the downregulation of MMP-9 by fenofibrate would be expected to inhibit aortic destruction in addition to limiting activation of important pro-inflammatory cytokines, such as OPN.

Kallistatin is a serine proteinase inhibitor, known to be expressed in endothelial cells and vascular smooth muscle cells.[33] Overexpression of human kallistatin in rodent models has been shown to promote vasodilation.[34] More recently, kallistatin has been shown to limit a range of mechanisms implicated in AAA pathogenesis, such as inflammation, oxidative stress, angiogenesis, and hypertension.[35-43] Thus, identifying treatments that upregulate kallistatin may be of benefit in the clinical management of AAAs. The effect of fenofibrate on serum kallistatin levels in humans has not previously been investigated.

Overall, a large body of data suggests fenofibrate can inhibit key pathological mechanisms involved in human AAA progression. The aim of the current study is to assess the effect of fenofibrate taken daily for 24 weeks in participants with small AAAs (35-49 mm) on key pathological markers of AAA. The primary aims are to determine whether fenofibrate will reduce the serum concentrations of OPN, and increase the serum concentration of kallistatin. The effect of fenofibrate on secondary parameters including serum resistin concentration, serum lipids (total cholesterol, triglycerides, HDL and LDL), plasma MMP-9 concentration, other inflammatory markers (such as neutrophils, C-reactive protein, cell markers for T cells, B cells and neutrophils), and circulating concentrations of AAA biomarkers will also be assessed. Finally, AAA diameter will be assessed at entry and 6 months by ultrasound.

METHODS

Study design and participants

Fenofibrate in the management of AbdoMinal aortic anEurysm (FAME)-2 is a multi-centre, prospective, randomised, double-blind, placebo-controlled clinical trial to assess the effect of 24 weeks of oral therapy with 145 mg of fenofibrate on circulating pathological markers of AAA. The trial will be conducted at four sites in Australia: The Royal Brisbane and Women's Hospital, Brisbane; The Townsville Hospital, Townsville; Gosford Vascular Services, Gosford and Mackay Base Hospital, Mackay. The trial was registered on 18 September 2013 with the Australian New Zealand Clinical Trials Registry (ACTRN 12613001039774). The trial has received multicentre ethical approval from The Prince Charles Hospital Human Research Ethics Committee (HREC/13/QPCH/16) for all four sites. The trial will be conducted in agreement with the principles of the Declaration of Helsinki. All participants will be informed about the purpose of the trial, the risks and benefits, and written informed consent will be obtained prior to entry by the local study coordinator. Only research personnel who are directly involved in the recruitment and data collection aspect of the study will have access to patient's personal details. All case report forms (CRF's), source documentation and samples will be stored de-identified where personal information has been removed and coded with a study number.

The FAME-2 trial will include participants recruited from specialist vascular outpatient clinics who provide written

informed consent and have an infrarenal AAA measuring a maximum orthogonal diameter of 35-49 mm. FAME-2 will not include individuals with a current indication for AAA repair or expectation that this will be revised within 6 months. Furthermore, participants will only be included if they have a high likelihood of treatment compliance over 24 weeks. Additional exclusion criteria include known contraindications to fenofibrate treatment and previous infrarenal abdominal aortic surgery. A full list of inclusion and exclusion criteria is given in Table 1.

Table 1: Patient eligibility criteria.

Inclusion Criteria
• Written informed consent • Infrarenal AAA measuring a maximal orthogonal diameter of 35-49 mm on CTA or ultrasound • No current indication for AAA repair according to treating physician or expectation that this will be revised within 6 months • High likelihood of compliance with treatment over 24 weeks according to treating physician
Exclusion Criteria
• Currently taking fenofibrate or related fibrates • Contraindication to fenofibrate treatment: 1. Liver impairment as demonstrated by abnormal AST or ALT tests (> 1.5 x ULN) 2. Renal impairment as demonstrated by an elevated serum creatinine level (> 150 µM) 3. Symptomatic gallbladder disease 4. Previous reaction to any lipid modifying medication • Previous infrarenal abdominal aortic surgery • Symptomatic, ruptured or mycotic AAA • Current participation in another drug trial

CTA- computed tomographic angiography; AAA- abdominal aortic aneurysm; AST- aspartate aminotransferase; ALT- alanine transaminase; ULN- upper limit of normal.

Randomisation and follow-up

The overall design of the FAME-2 trial is shown in Table 2. During vascular outpatient clinics, potential participants will be pre-screened for suitability and if appropriate, informed consent will be obtained. Subsequently, potential participants will be assessed against the eligibility criteria during the initial visit as in Table 1. Individuals will undergo an ultrasound of their infrarenal aorta, a medical examination, anthropometric assessment (height, weight, waist and hip circumference), resting blood pressure, heart rate and ankle-brachial index assessments, a quality of life questionnaire, and collection of blood samples for measurement of full blood count (haemoglobin, white cell count, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils), urea and electrolytes (sodium, potassium, creatinine, estimated glomerular filtration rate, albumin, total bilirubin, urea, chloride, bicarbonate), liver function tests (alanine transaminase, aspartate aminotransferase, gamma-glutamyl transpeptidase, lactate dehydrogenase), bleeding studies (international normalised ratio, prothrombin time, activated partial thromboplastin time, fibrinogen), fasting lipids (cholesterol, triglyceride, HDL cholesterol, low density lipoprotein cholesterol), fasting glucose, C-reactive protein and homocysteine. Serum, plasma and whole blood will also be collected for assessment of proteins (cytokines) in circulation and genetic (DNA and RNA) analysis.

Blood samples will be processed according to site-specific standard operating procedures (SOPs) and shipped to the study centre in Townsville. Eligible participants will be randomised to receive 145 mg fenofibrate or placebo, orally once per day, for 24 weeks, in a parallel group design. Randomisation to fenofibrate or placebo will be stratified by study centre and aortic diameter (35-39, 40-44, 45-49 mm).

Table 2: Summary of assessments.

	Study time-points (weeks)				
Assessment	0 Visit 1	0 Visit 2	3 Phone call	12 Phone call	24 Visit 3
Consent	X				
Enrolment/Randomisation		X			
Medical examination	X				X
SF-36 questionnaire	X				X
Ultrasound	X				X
Blood test (safety)	X		X		X
Blood collection (study)	X		X		X
Resting ABI	X				X
Physical assessments	X				X
Collection of medication		X			
Return of medication					X
Drug safety / compliance check			X	X	X
Recording of adverse events			X	X	X

Physical assessments include: resting blood pressure and heart rate, height, weight, waist and hip measurements. ABI- ankle brachial index; SF-36- short form 36.

Random allocation sequences will be computer generated by a statistician and maintained at the central medication centre, ensuring both investigators and participants are blinded to drug assignment.

Trial medication will be allocated and dispensed by the local study centre clinical trials pharmacist by telephone call. Allocation concealment will be achieved by using identical packaging of intervention and placebo. In the case of an emergency situation where breaking of the group allocation blinding would be required, the clinical trial pharmacist at the central medication centre will be contacted. To facilitate compliance, participants will be provided with the phone number of the local study coordinator with instructions to contact in the event of possible medication related problems or consideration of discontinuation. In this event arrangements will be made for the participant to be reviewed by the study physician to ascertain if discontinuation is required. Following randomisation, participants will receive their allocated study medication with instruction regarding dosing regimen. Participants will be contacted by telephone calls at 3 and 12 weeks after commencement of medication and asked about adherence to the study drug regimen as well as adverse and clinical events. An additional blood test and collection will be performed at 3 weeks, as per the initial visit and to assess for safety. All participants, including those in whom medication is ceased due to adverse events, will be invited to follow-up for the duration of the study in the absence of AAA repair. Final follow-up will occur at 24 weeks after commencement of medication, according to Table 2, at which point the participant will discontinue the study medication. Compliance with the study medication will be analysed by capsule and bottle counting.

Outcome assessment

Primary and secondary outcome measures will be assessed in blood samples and by AAA imaging at baseline and 24 weeks as summarised in Table 3. At baseline, 3 and 24 weeks, fasting serum, RNA and plasma samples will be obtained, analysed or immediately aliquoted and stored at -80°C for later bulk analysis. AAA diameter will be measured by ultrasound imaging. Reproducible techniques have been established to quantify all the primary and secondary outcomes in previous studies. RNA will be extracted from total blood using previously described methods and stored for future microarrays to enable hypothesis generating analyses.[44] Outcome assessment will be performed at the study centre in Townsville on the tissue and blood samples collected. All outcome assessment will be conducted by scientists blinded to the treatment allocation of the participants.

Primary outcome assessment

Serum OPN and kallistatin concentrations will be assessed on stored serum using the Quantikine R&D Systems ELISA (Minneapolis, USA) according to manufacturer's instructions. The accuracy of this assay in measuring serum OPN has previously been assessed. Linearity of standards and serum using doubling dilution was excellent (R2 0.99), and intra- and inter-assay reproducibility were good (concordance correlation coefficients 0.997 and 0.929).[12]

Table 3: Summary of primary and secondary endpoints.

Primary endpoint	Measurement method
Serum OPN concentration (ng/ml)	ELISA
Serum kallistatin concentration (ng/ml)	ELISA
Secondary endpoint	**Measurement method**
Serum HDL concentration (mM)	Automated assays
Plasma MMP-9 (ng/ml)	ELISA
Serum resistin (ng/ml)	ELISA
Other inflammatory markers	ELISA, flow cytometry, microarrays and real time PCR

OPN- osteopontin; ELISA- enzyme-linked immunosorbent assay; HDL- high-density lipoprotein; MMP-9- Matrix metallopeptidase 9; PCR- polymerase chain reaction

Secondary outcome assessment

Serum resistin concentration will be assessed using the Quantikine R&D Systems ELISA (Minneapolis, USA) according to manufacturer's instructions and expressed as nanogram per millilitre. Intra-assay and inter-assay coefficients of variation for this assay are between 3% and 6% (concordance correlation coefficients ~0.99).[22] Serum lipids, including total cholesterol, triglycerides, LDL and HDL will be assessed on serum obtained from participants who have fasted overnight using automated assays (Hitachi 917, Roche Diagnostics GmBH, Mannheim, Germany). The inter-assay coefficients of variations for these assays have been between 2% and 5% in previous studies.[22] Plasma MMP-9 concentration will be measured using Quantikine R&D Systems ELISA, as this has previously been shown to be reproducible.[45] Full blood count and C-reactive protein, will be assessed as previously described.[46] Microarrays and real time PCR will be used to assess circulating cell markers as previously described.[47]

Ultrasound measurements will be undertaken at entry and 24 weeks by experienced sonographers within the vascular laboratories at each study centre. The sonographers will measure the maximum diameters of the infrarenal aorta perpendicular to blood flow while the participant is in supine and lateral decubitus position. The sonographers will measure the diameter two ways; between the aortic intima and between the aortic adventitia providing an inner-to-inner and outer-to-outer

measurement respectively. While the participant is in the supine position the sonographer will measure anteroposterior and transverse aortic diameters and measure anteroposterior aortic diameter only while the participant is in the lateral decubitus position. The sonographer will also measure the maximum outer-to-outer anteroposterior common iliac diameters while the participant is in the supine position. Static DICOM images will be copied by the sonographer, with all measurement callipers in place, and sent to the central study centre where they will be centrally read by an experienced reader at completion of the study.

Additional outcome measures include change in resting brachial blood pressure, resting ankle-brachial index and health-related quality of life, as assessed by the Short Form-36 (SF-36) questionnaire. Finally, requirement for AAA surgery, AAA rupture, all-cause mortality, acute cardiovascular events, withdrawal from study medication, drug safety and changes in background medication will be recorded.

Study population and power calculation

The estimated primary outcomes for the placebo group are based on assessments performed in human AAA blood samples in previous studies.[12,21,22,24] It is hypothesised that administration of 145 mg of fenofibrate daily for 24 weeks will result in a 30% increase in serum kallistatin and a 30% reduction in serum OPN concentrations. These conservative estimates are based on previous findings that fenofibrate increases secretion of kallistatin by ~300% in aortic VSMC in vitro and reduces aortic OPN concentration by ~95% in a mouse model of AAA.[9] They also take into account the reported ability of a fibrate to reduce circulating OPN concentration by ~23%.[17] Allowing for a drop-out rate of 20%, a total of 60 patients per group are required (90% power and alpha 0.025, using nQuery Advisor).

In May 2015 after approximately half the planned participants had competed the study, drug compliance was analysed by capsule counting and assumed when a participant had consumed at least 95% of the planned tablets by completion of the study. At that point, 79% of participants were deemed compliant. In view of this, the planned recruitment target was increased by 20 participants to minimize the risk of being under powered to test the primary hypothesis of the trial.

Safety

Outside of its current indication of high serum triglyceride, the largest source of available data on fenofibrate safety derives from the FIELD study.[19] In that study, 9795 individuals with type 2 diabetes mellitus were randomly assigned to receive either fenofibrate or placebo for 5 years to assess its effect on cardiovascular disease events. Participants were administered a 200 mg micronised dose of fenofibrate which is equivalent to the 145 mg capsule used in FAME-2. The FIELD study demonstrated a reduction in total cardiovascular events for participants assigned to fenofibrate, as well as a significantly reduced rate of progression to albuminuria. No significant differences were found between the incidence of laboratory abnormalities, minor possible drug reactions or possible serious adverse drug reactions between the two groups. The median serum creatinine of patients taking fenofibrate was 91 versus 80 μM in control subjects at the close of study, $p < 0.001$. Creatinine was shown to fall by a median of 15 μM in 661 patients investigated 8 weeks after ceasing medication. Conversely, participants assigned to fenofibrate were found to have a slowed estimated GFR loss over 5 years.[48] Based on the FIELD study data, it is assessed that administration of 145 mg fenofibrate daily is likely to be associated with very few serious side effects in the FAME-2 study.

Participant safety will be assessed prior to the administration of the medication and at 3 and 24 weeks. At the initial visit, a consultation with a physician will occur, during which the participant will be informed about known side effects including symptoms of abdominal/back pain, chest pain and muscle aching. Pathology tests consisting of full blood count, fasting lipids, glucose, inflammation markers, liver and renal function will be performed.

Physical assessments including blood pressure and heart rate will be reviewed by a medical officer along with the results of the pathology tests prior to randomisation. At 3 and 24 weeks, pathology tests as per the initial visit will be performed and reviewed by a medical officer. Any adverse event will be reported to the coordinating centre and carefully monitored throughout the study. Serious adverse events (SAEs) will be defined as death, medically important, requirement for in-patient hospital treatment and persistent of significant disability. All SAEs will be reported by the site principle investigator to HREC and reviewed by the chief principle investigator, where a decision regarding withdrawal of trial medication will be made. Where a decision to withdraw trial medication is made, participants will be encouraged to remain on the study protocol.

Data management and analysis

The data management committee will comprise the chief investigators at each of the sites involved. Trial documentation including protocols, SOPs and CRFs will be shared electronically with participating study centres. Protocol amendments will be submitted to The Prince Charles Hospital HREC and local site Research Governance offices, and disseminated to the relevant parties at each study site. Data recorded on printed CRFs will be scanned to the study centre in Townsville where it will be entered centrally and examined for data quality. This will allow confirmation of entry criteria, and collection of set entry and outcome data. Examples of

important baseline data which will be collected include age, gender, risk factors, concurrent medications and morphology of the AAA assessed from ultrasound. Definitions and accurate methods to quantify these data have been developed in previous studies.[22,24] At completion of the trial the database will be checked for errors and data confirmed with source documentation where required. Analysis of primary and secondary endpoints will be based on intention to treat at the time of randomisation.

All participants who meet the eligibility criteria, provide written informed consent and are enrolled in the study will be included in the primary analysis, regardless of adherence to medication allocation. Data will be analysed with appropriate non-parametric or parametric tests depending on data distribution and, if appropriate, multivariate tests such as logistic regression will be used to adjust for confounding factors. Data will be published in a peer-reviewed journal with copies of the paper available to participants if required.

DISCUSSION

There is no known effective medical therapy to limit AAA growth, and to date large randomised controlled trials have failed to report the benefit of any tested agent.[49-52] Furthermore, early elective endovascular repair or open surgery for patients with AAAs measuring 40-54 mm has not been found to improve mortality rates.[53-56] Identification of a novel therapy to limit AAA expansion would represent a significant breakthrough in the clinical management of this disease. In the current study the effect of a promising new medical therapy will be assessed.

The study has been specifically designed to determine whether findings in rodent models can be confirmed in patients, and will enable the determination of whether: a) fenofibrate can rapidly inhibit key pathological mechanisms of AAA progression; b) the efficacy of fenofibrate in limiting AAA inflammation can be monitored in blood samples. Thus, FAME-2 has the potential of identifying a medication which can limit key pathological mechanisms in AAAs and may offer a means to monitor efficacy of the drug via a simple blood test. If findings from this pilot study are positive, larger trials will be needed to examine the benefit of fenofibrate over longer follow-up in a larger cohort of patients.

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Conflict of interest: None declared

Ethical approval: The study was approved by The Prince Charles Hospital Human Research Ethics Committee (HREC/13/QPCH/16) for all four sites

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