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Protocol of the Febuxostat versus Allopurinol Streamlined Trial (FAST): a large prospective, randomised, open, blinded endpoint study comparing the cardiovascular safety of allopurinol and febuxostat in the management of symptomatic hyperuricaemia

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ABSTRACT

Introduction: Gout affects 2.5% of the UK's adult population and is now the most common type of inflammatory arthritis. The long-term management of gout requires reduction of serum urate levels and this is most often achieved with use of xanthine oxidase inhibitors, such as allopurinol. Febuxostat is the first new xanthine oxidase inhibitor since allopurinol and was licensed for use in 2008. The European Medicines Agency requested a postlicensing cardiovascular safety study of febuxostat versus allopurinol, which has been named the Febuxostat versus Allopurinol Streamlined trial (FAST).

Methods and analysis: FAST is a cardiovascular safety study using the prospective, randomised, open, blinded endpoint design. FAST is recruiting in the UK and Denmark. Recruited patients are aged over 60 years, prescribed allopurinol for symptomatic hyperuricaemia and have at least one additional cardiovascular risk factor. After an allopurinol lead-in phase where the dose of allopurinol is optimised to achieve European League against Rheumatism (EULAR) urate targets (serum urate <357 µmol/L), patients are randomised to either continue optimal dose allopurinol or to use febuxostat. Patients are followed-up for an average of 3 years. The primary endpoint is first occurrence of the Anti-Platelet Trialists' Collaboration (APTC) cardiovascular endpoint of non-fatal myocardial infarction, non-fatal stroke or cardiovascular death. Secondary endpoints are all cause mortality and hospitalisations for heart failure, unstable, new or worsening angina, coronary or cerebral revascularisation, transient ischaemic attack, non-fatal cardiac arrest, venous and peripheral arterial vascular thrombotic event and arrhythmia with no evidence of ischaemia. The primary analysis is a non-inferiority analysis with a non-inferiority upper limit for the HR for the primary outcome of 1.3.

Ethics and dissemination: FAST (ISRCTN72443728) has ethical approval in the UK and Denmark, and results will be published in a peer reviewed journal.

Trial Registration number: FAST is registered in the EU Clinical Trials Register (EUDRACT No: 2011-001883-23) and International Standard Randomised Controlled Trial Number Register (ISRCTN No: ISRCTN72443728).

Strengths and limitations of this study

- Use of technology including an electronic case report form, web portal and record linkage to identify potential endpoints provides efficient data management.
- The open-label design provides good external validity as the trial is conducted in the normal care setting. The endpoint committee is blinded to randomised treatment.
- A minor study limitation will be the non-inclusion of younger populations with hyperuricaemia.

INTRODUCTION

Gout is the commonest inflammatory arthropathy in men over the age of 40, and current prevalence is estimated at 1–2% of the adult population in western countries with UK prevalence of 2.5%.[1–4] Gout is characterised by the deposition of monosodium urate

crystals in joints and other tissues, causing an acutely painful inflammatory arthritis that can progress to a chronic and disabling destructive arthropathy. Crystal deposition in soft tissues may also be seen as gouty tophi. Although serum urate levels correlate poorly with disease activity, hyperuricaemia is the most significant risk factor for the development of symptomatic gout. Hyperuricaemia is generally defined as urate above approximately 400 µmol/L (6.8 mg/dL), as this is the concentration at which uric acid becomes insoluble in plasma.[5]

It is well recognised that patients with gout have increased cardiovascular morbidity and mortality compared with the general population, and urate levels are increasingly believed to be an independent predictor of cardiovascular mortality. Theories as to the specific causal relationship between hyperuricaemia and cardiovascular disease/mortality vary; however, the correlation between the two is widely recognised. It is also not clear whether lowering urate levels would improve the cardiovascular event rate of patients with hyperuricaemia.[6–9]

Management of gout was revolutionised in the 1960s with the introduction of allopurinol, the first xanthine oxidase inhibitor, which reliably reduced urate levels, gout flares and long-term complications of gout.[10] The current European League against Rheumatism (EULAR) guideline for the management of gout recommends that urate lowering therapy (ULT) is indicated in patients with recurrent acute flares, arthropathy, tophi or radiographic changes of gout. The therapeutic goal of ULT is to promote crystal dissolution and prevent crystal formation. This is achieved by maintaining the serum urate level (SUA) below the saturation point for monosodium urate, and the target level recommended is <357 µmol/L (<6 mg/dL).[11] Allopurinol is currently the first-line ULT in the UK and Europe. It is licensed in the dose range of 100–900 mg; however, patients with renal impairment are recommended to take the minimum effective dose required to achieve urate control.[12] In the UK, the majority of patients are prescribed between 100 and 300 mg of allopurinol daily, and primary care surveys have shown that the EULAR guideline target for urate is achieved in less than 50% of patients with gout receiving 300 mg of allopurinol.[13]

Febuxostat is a novel xanthine oxidase inhibitor which was licensed in 2008 for the treatment of chronic hyperuricaemia in conditions where urate deposition has occurred. The febuxostat Phase III randomised controlled trials demonstrated that 80 mg febuxostat was superior to allopurinol 300 mg in achieving and maintaining the target urate level of <357 µmol/L.[14] Febuxostat can also be prescribed to patients with mild-to-moderate renal insufficiency without the need for dose adjustment, and therefore provides an important alternative in the treatment of hyperuricaemia in patients with gout with renal impairment.

In the Phase III and long-term clinical extension studies of febuxostat, there was a numerical increase in investigator-reported cardiovascular events with febuxostat when compared to allopurinol. However, no statistically significant differences were found, no causal relationship was established and 60% of the patients in these trials had ≥2 risk factors for cardiovascular disease. The European Union Risk Management Plan for febuxostat (V.2.0; 19 February 2008) indicated that a postmarketing study to evaluate cardiovascular safety of febuxostat was to be conducted as part of the febuxostat pharmacovigilance plan. To fulfil this postlicensing obligation, a large safety study of febuxostat versus standard ULT with allopurinol for patients with symptomatic hyperuricaemia (gout) is being undertaken. The study is named the FAST.

METHODS

Trial design

Overall trial design

FAST is a prospective, randomised, open-label, blinded endpoint evaluation (PROBE) design trial to compare the cardiovascular safety of febuxostat and allopurinol. The PROBE design allows the real-world use of the two drugs to be compared, and also allows for dose adjustments during the study, if required.[15] Recruited patients are randomised to either allopurinol or febuxostat and followed-up for a minimum of 3 years.

Study population

FAST has study centres in Scotland, England and Denmark. Each centre identifies regional general practices to act as study sites and potential study patients are recruited from these study sites. General practice patient lists are searched for patients aged 60 years or more who are taking chronic allopurinol (defined as 60 days or 2 or more prescriptions for allopurinol in the last 6 months). Patients meeting these selection criteria have their case records reviewed by appropriately trained staff to determine eligibility according to inclusion and exclusion criteria (detailed in boxes 1 and 2). Patients identified as potentially suitable are provided with written study information and invited to attend a screening visit.

Consent

Written, informed consent is obtained at the screening visit for all patients who wish to proceed in the study. Screening visits are conducted by research nurses with appropriate training in obtaining informed consent.

Randomisation

Randomisation is performed through a central web-based randomisation facility located at the Robertson Centre for Biostatistics, University of Glasgow. Randomisation is stratified according to previous cardiovascular events (myocardial infarction (MI), stroke or hospitalisation for congestive heart failure or peripheral vascular disease).

Data storage—electronic clinical report form

Patient data are entered via a secure web-based electronic clinical report form (eCRF) with a central database at the Robertson Centre for Biostatistics, University of Glasgow.

Trial treatments

Trial treatments are allopurinol or febuxostat. Allopurinol dose is determined during the allopurinol lead-in phase (see below) and febuxostat is started at 80 mg daily with potential to increase to 120 mg daily if SUA is above the EULAR target at a 2 week check. The allopurinol lead-in phase is required because febuxostat 80 mg is a more potent urate lowering therapy than low dose allopurinol. A study overview is shown in figure 1.

Trial medication is supplied directly to each patient by post from the Dundee University Research Pharmacy. All trial medication is supplied open-label.

Allopurinol lead-in phase

An allopurinol lead-in phase precedes randomisation. If the SUA exceeds the EULAR recommended target of <357 µmol/L on screening blood tests, the daily allopurinol dose is increased by 100 mg. SUA levels are rechecked after 2 weeks on the higher dose and this process is repeated until the EULAR target is achieved or the maximum tolerated dose of allopurinol is reached. If SUA at screening is <357 µmol/L then no dose titrations are required and the patient proceeds straight to randomisation. Patients with renal impairment (estimated-glomerular filtration rate 30–60 mL/

Box 1 FAST inclusion criteria

Inclusion criteria

1. Male or female patients aged 60 years or older with at least one additional cardiovascular risk factor:
   - Age ≥70 years (male) or ≥75 years (female)
   - Smoking (current or within the last 2 years)
   - Diabetes mellitus
   - Impaired glucose tolerance
   - Hypertension (systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg) or receiving treatment to lower blood pressure
   - Dyslipidaemia (investigator assessment)
   - Chronic kidney disease
   - Microalbuminuria or proteinuria
   - Family history of coronary heart disease or stroke in first-degree relative at age <55 years
   - Inflammatory arthritis (investigator assessment—including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis)
   - Chronic non-steroidal anti-inflammatory drugs therapy (investigator assessment)
   - Previous cardiovascular event (myocardial infarction, cerebrovascular accident or transient ischaemic attack)
   - Peripheral vascular disease (investigator/clinical assessment)
   - Chronic obstructive pulmonary disease
   - Body mass index >30 kg/m^2
2. Patients who, in the opinion of the recruiting physician, require treatment for chronic hyperuricaemia where urate deposition has already occurred (including a history or presence of tophus and/or gouty arthritis) fulfilling the recommendation for treatment with urate lowering therapy.
3. Patients who have received ≥60 days treatment with allopurinol, or ≥2 allopurinol prescriptions, within the previous 6 months.
4. Patients, who in the opinion of the recruiting physician or study site coordinator, are eligible for treatment (with reference to the summary of product characteristics) with either allopurinol or febuxostat.
5. Patients who are willing to give permission for their paper and electronic medical records, hospitalisation data, prescribing data and (in the event of their death) their death certification data to be accessed and abstracted by trial investigators.
6. Patients who are willing to be contacted and interviewed by trial investigators or delegates (suitably trained research nurses), should the need arise (eg, for adverse event assessment and to determine whether an episode of acute gout has occurred).

Box 2 FAST exclusion criteria

Exclusion criteria

1. Patients who have any contraindication to febuxostat or allopurinol (with reference to the summary of product characteristics) or any of the components of their formulations.
2. Patients who are not receiving allopurinol as urate lowering therapy.
3. Patients with severe renal impairment (estimated-glomerular filtration rate <30 mL/min as defined by the Cockroft-Gault formula (http://www.nephron.com/cgi-bin/CGSI.cgi) according to creatinine, age, sex and body weight).
4. Patients with moderate or severe hepatic impairment, that is, cirrhosis with clinical and/or biological decompensation (ie, alanine aminotransferase or aspartate aminotransferase >3× reference value, ascites, lower limb oedema, icterus or increased prothrombin time >2× reference value).
5. Patients with a life-threatening comorbidity or with a significant medical condition and/or conditions that would interfere with the treatment, safety or compliance with the protocol.
6. Patients with a diagnosis of, or receiving treatment for, malignancy (excluding minor skin cancer) in the previous 5 years.
7. Patients who have experienced either a myocardial infarction or stroke within the 6 months prior to the screening visit.
8. Patients with congestive heart failure, New York Heart Association (NYHA) Class III or IV.
9. Patients whose behaviour or lifestyle would render them less likely to comply with study medication (ie, abuse of alcohol, substance misuse, debilitating psychiatric conditions or inability to provide informed consent).
10. Patients with a current acute gout flare or who are within 14 days of the resolution of a gout flare.
11. Patients currently participating in another clinical trial or who have participated in a non-interventional clinical trial in the previous 1 month or an interventional clinical trial in the previous 3 months.

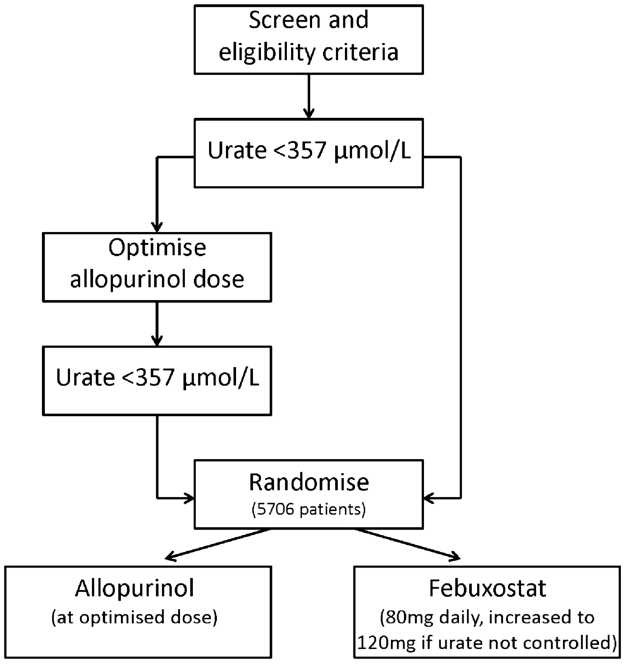

Figure 1 Overview of the FAST trial.

min) have their allopurinol dose titrated in exactly the same manner as those without renal impairment. This reflects published guidance on allopurinol titration in renal impairment which recommends starting at a low dose and titrating to achieve urate target.[16]

Allopurinol washout

Once patients are randomised and prior to start of randomised treatment all patients have an allopurinol washout period of at least 7 days (window 7–21 days).

Gout flare prophylaxis

Patients requiring up-titration of allopurinol during the allopurinol lead-in phase and all patients postrandomisation are offered gout flare prophylaxis. First-line prophylaxis is with colchicine (0.5 mg once or twice daily) and second-line alternatives are non-steroidal anti-inflammatory drugs (NSAID's; naproxen, diclofenac or meloxicam) with gastric protection. Prophylaxis postrandomisation is offered for 6 months. Patients may decline prophylaxis or discontinue prophylaxis at any time and prophylaxis may be tailored by the patients' primary care physician, particularly if there are concerns with long-term NSAID use. General practitioners (GPs) are left to manage gout flares according to local guidelines.

Postrandomisation treatment

Patients randomised to allopurinol continue to receive allopurinol at the dose determined before randomisation (ie, the dose required to achieve SUA level <357 µmol/L or the maximum tolerated dose). Patients randomised to febuxostat will start with 80 mg daily with potential to increase the dose to 120 mg if the SUA is ≥357 µmol/L after 2 weeks.

All drugs supplied to randomised patients from the Dundee University Research Pharmacy are recorded on the patient's eCRF, providing a cumulative record of supplied and returned medications.

Efficacy

If therapeutic efficacy is judged to be inadequate, physicians have the option to increase the dose of study medication according to their clinical judgment and EULAR recommendations provided this remains in line with the current summary of product characteristics for allopurinol and febuxostat. GPs are also free to decrease the dose of either drug if appropriate. Changes in dose are recorded in the eCRF.

Tolerability

Patients who experience any treatment-related adverse events may have their dosage adjusted or trial medication stopped according to clinical judgment. Study personnel report such events as adverse reactions (with severity assessment) as appropriate.

Follow-up

Patients will be followed-up for an average of 3 years from randomisation. Contact will be made by study nurses every 2 months by phone, letter or visit to the patient. Every patient will be seen annually and annual visits will include clinical review and annual blood testing for SUA level, renal and liver function. Recruiting physicians and the patients' GP may also report any significant events and adverse events thought to be related to study medication at any time during the follow-up period.

Record linkage is available in Scotland, England and Denmark and refers to the method by which patient-specific information that is stored separately can be linked to provide comprehensive patient data for hospitalisations and deaths.[17] Record linkage will be performed at regular intervals during FAST follow-up.

Trial endpoints

Primary endpoint

The primary endpoint is the first occurrence after randomisation of any event included in the Anti-Platelet Trialists' Collaboration (APTC) composite endpoint (hospitalisation for non-fatal MI/biomarker positive acute coronary syndrome, non-fatal stroke (whether reported to have been hospitalised, non-hospitalised or to have occurred during a hospitalisation) or death due to a cardiovascular event).[18]

Secondary endpoints and further planned exploratory analysis are detailed in box 3.

Assessment of endpoints, adverse events and serious adverse events

All observed or volunteered adverse events that are considered to be either serious or related to study treatment (or both) are recorded in the eCRF. Physicians assess

Box 3 FAST secondary and exploratory endpoints

Secondary endpoints

The following secondary endpoints (in rank order of importance) will be evaluated using a time to event analysis:

- Hospitalisation for non-fatal myocardial infarction/biomarker positive acute coronary syndrome
- Non-fatal stroke (whether reported to have been hospitalised, non-hospitalised or to have occurred *during* a hospitalisation)
- Cardiovascular death
- All cause mortality
- Hospitalisation for heart failure
- Hospitalisation for unstable, new or worsening angina
- Hospitalisation for coronary revascularisation
- Hospitalisation for cerebral revascularisation
- Hospitalisation for transient ischaemic attack
- Hospitalisation for non-fatal cardiac arrest
- Hospitalisation for venous and peripheral arterial vascular thrombotic event
- Hospitalisation for arrhythmia with no evidence of ischaemia

The following endpoints will be evaluated as an incidence rate:

- Cardiovascular mortality
- Anti-Platelet Trialists' Collaboration events in each treatment arm

Exploratory efficacy endpoint

The proportion of patients whose urate level is ≥6.0, <6.0 and <5.0 mg/dL after 1, 2 and 3 years of treatment.

the causality and expectedness of any event thought to be related to one of the study medications. An event is deemed serious if it results in death, is life-threatening, requires hospitalisation, results in persistent or significant disability/incapacity or any other important medical event that requires medical or surgical intervention to prevent serious outcomes (whether or not the event was related to study medication). Serious adverse events (SAEs) are reported by study personnel without delay and are also collected regularly where appropriate using record-linkage methods. SAEs are followed up until resolved or the patient has died. Events that are neither serious nor related to study medication are not required to be reported. Primary and secondary study endpoints and their associated symptoms or laboratory abnormalities are not reported as suspected unexpected serious adverse reactions (SUSARs).

If a reported SAE is a potential study endpoint, more detailed information is collected and an anonymised endpoint package is prepared. Endpoint data are adjudicated by an independent endpoint committee blinded to randomised treatment.

DATA ANALYSIS AND STATISTICAL METHODS

Sample size

A total of 456 APTC events are required to show non-inferiority between the febuxostat and allopurinol treatment arms assuming non-inferiority limit for the HR (febuxostat vs allopurinol) of 1.3, with 80% power and a one-sided α of 0.025. Non-inferiority will be claimed if the upper limit of the 95% CI for the HR is ≤1.3 for the per-protocol analysis.

Assuming a cardiovascular event rate at 3 years in the allopurinol treatment arm is estimated at 10%,[i] then 2282 patients will be required in each treatment arm to detect the 456 events. Allowing for a loss of follow-up due to non-cardiovascular death, withdrawal of consent or other loss to follow-up, we intend to recruit an additional 20% of patients to a total of 5706 patients with 2853 patients in each treatment arm.

Primary analysis

A full statistical plan is developed for the primary analysis. Time to event analysis will involve Cox proportional hazards models including the randomised treatment group and randomisation strata (previous cardiovascular events (yes/no) as covariates). Statistical significance for effect will be based on the Wald statistic with associated 95% CIs for the estimated HR comparing febuxostat to allopurinol.

The first analysis to be carried out will be a non-inferiority analysis of the primary outcome based on the per-protocol population (those patients remaining on randomised therapy) with a supporting non-inferiority analysis based on the intention-to-treat (ITT) population. Per-protocol analysis will exclude patients who discontinued trial therapy, deaths from non-cardiovascular causes and patients lost to follow-up. If non-inferiority is demonstrated, a superiority analysis will be carried out based on the ITT population.

Sensitivity analysis

A sensitivity analysis will be performed by censoring patient follow-up at 90 days beyond the per-protocol period or end of study, whichever comes first. This will be performed for primary and secondary endpoints.

To adjust for the possibility of differential drop-out in the per-protocol analysis, a further analysis will be carried out adjusting for age, sex, LDL-cholesterol levels and HDL-cholesterol levels, systolic blood pressure, smoking status and histories of diabetes, hypertension and cardiovascular disease.

ETHICS AND DISSEMINATION

Steering Committee and Independent Data Monitoring Committee

A Steering Committee oversees the conduct of the trial. An independent Data Monitoring Committee receives unblinded data and has the power to recommend modifications to the conduct of the study, including early

[i]Cardiovascular event rate was calculated using cohorts of patients from the Tayside Medicines Monitoring Unit database who were dispensed allopurinol in Scotland between 1994 and 2002 and cardiovascular events and deaths occurring in these patients up to 2002 from the Scottish Morbidity Record One and General Registrar Office database.

discontinuation based on a risk/benefit assessment of the study data.

Study sponsorship: monitoring, audit, quality control and quality assurance

The study sponsor is the University of Dundee which undertakes monitoring and quality assurance. The trial is funded by Menarini in partnership with Ipsen and Tejin.

Access to data

The completed, original eCRF data will be the joint property of the University of Dundee and the University of Glasgow. Data will be available for authorised representatives of the universities or regulatory authorities or to third parties with express written permission from the universities.

Ethics

FAST is registered as ISRCTN72443728. The trial is performed in line with Good Clinical Practice guidelines and International Society of Pharmacoepidemiology (ISPE) Good Pharmacoepidemiology Practice guidance.[19]

Dissemination

The results of the trial will be published in a peer-reviewed scientific journal and presented at a major conference.

DISCUSSION

The trial design of FAST allows a large safety study to be undertaken with efficient use of resources by maximising the benefits of modern technology including use of an eCRF and following up patients using record linkage. The trial design has good external validity by comparing drugs in a real-world setting and evaluating outcomes in the patient population most likely to be taking these drugs.

The Dundee University Research Pharmacy is the first purely research pharmacy in the UK and allows all trial medication to be posted directly to patients in the UK and Denmark. This is advantageous for the patient and their primary care physician, and allows tracking of drug supply and drug return.

When completed, FAST will help to establish the cardiovascular safety of febuxostat and allopurinol in a population with high cardiovascular risk. Efficacy endpoints will also help to define the role of febuxostat in the management of patients with gout.

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Contributors The idea was conceived by TMM. The initial draft of the manuscript was created by CGJ and ISM and circulated among the authors for critical revision. The Chief Investigator of FAST is TMM. All authors approved the final version of the manuscript.

Competing interests TMM holds research grants from Novartis, Pfizer, Ipsen and Menarini, is currently or has been the principal investigator on trials paid for by Pfizer, Novartis, Ipsen and Menarini and TMM has been paid consulting or speakers fees by Pfizer, Novartis, Kaiser Permanante, Takeda, Recordati, Servier, Menarini, and AstraZeneca in the previous 3 years. ISM holds research grants from Novartis, Ipsen and Menarini.

Ethics approval The trial has been approved by the UK Multi-Centre Research Ethics Committee (Reference number: 2011-001883-23) and the Medicines and Healthcare Products Regulatory Agency (Reference number: 11/AL/0311) as well as the relevant authorities in Denmark.

Provenance and peer review Not commissioned; externally peer reviewed.

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