Long term cardiovascular safety of febuxostat in comparison with allopurinol in patients with gout: a multicentre, prospective, randomised, open-label, clinical trial. The Febuxostat versus Allopurinol Streamlined Trial (FAST).

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Summary

Background

Febuxostat and allopurinol are urate-lowering therapies used to treat patients with gout. Following concerns about the cardiovascular safety of febuxostat, the European Medicines Agency (EMA) recommended a post-licensing study comparing the cardiovascular (CV) safety of febuxostat versus allopurinol.

Methods

We conducted a prospective, randomised, open-label, blinded endpoint (PROBE) non-inferiority trial of febuxostat versus allopurinol in patients with gout in the UK, Denmark, and Sweden. Eligible patients were 60 years or older, currently treated with allopurinol, with at least one additional cardiovascular risk factor. After increasing allopurinol dose if necessary to achieve serum urate levels < 0·357 mmol/L (< 6 mg/dL), patients were randomly assigned to continue allopurinol (at optimised dose) or start febuxostat at a dose of 80mg daily, increasing to 120mg, if necessary, to achieve serum uric acid level < 0·357 mmol/L. The primary outcome was the composite of hospitalisation for non-fatal myocardial infarction/biomarker positive acute coronary syndrome, non-fatal stroke or cardiovascular death. The hazard ratio (febuxostat versus allopurinol) in a Cox proportional hazards model was assessed for non-inferiority (limit of 1·3) in an on-treatment (OT) analysis and then by intention to treat (ITT). This study is registered with the EU Clinical Trials Register (EudraCT 2011-001883-23) and ISRCTN (ISRCTN72443728).

Findings

From 20 December, 2011, to 26 January, 2018, 6128 patients (mean age 71, 85·3% male, 33·4% prior CV disease) were enrolled and randomised to receive allopurinol (n=3065) or febuxostat (n=3063)) and were followed up to December 2019, during which 5·5% and 6·2% respectively withdrew from all follow up. Median follow-up time in the study was 1467 days [IQR 1029-2052] and median on-

treatment follow-up period was 1324 days [IQR 870-1919]. In both the on-treatment and intention-to-treat analyses, febuxostat therapy was non-inferior to allopurinol therapy for incidence of the primary endpoint (OT analysis: febuxostat 172 patients [1·72 events per 100 patient years]; allopurinol 241 patients [2·05 events per 100 patient years]; hazard ratio 0·85 [95% CI 0·70-1·03], p<0·001; ITT analysis: febuxostat 256 patients [2·05 events per 100 patient years], allopurinol 285 patients [2·29 events per 100 patient years]; hazard ratio 0·89 [95% CI 0·75-1·06], p< 0·001). A total of 222 (7·2%) patients died and 1720 (57·3%) experienced at least one serious adverse event (SAE) in the febuxostat group compared to 263 deaths (8·6%) and 1812 patients with one or more SAE (59·4%) in the allopurinol group. In the febuxostat group, 973 patients [32·4%] discontinued randomised therapy compared with 503 patients [16·5%] on allopurinol.

Interpretation

Febuxostat was non-inferior to allopurinol therapy for the primary cardiovascular outcome. Long-term use of febuxostat was not associated with an increased risk of death or serious adverse events compared with allopurinol.

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Research in context

Evidence before this study

We searched PubMed on 17 September, 2020, using the search terms “febuxostat”, “allopurinol”, and “cardiovascular outcomes”. We searched for original articles with no date or language restriction for any randomised clinical trials with >500 participants comparing febuxostat with allopurinol in terms of cardiovascular outcomes. We found one trial, the ‘Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout (CARES)’ trial. This trial, involving 6190 randomised patients with gout and major cardiovascular coexisting conditions, reported that febuxostat was non-inferior to allopurinol with respect to rates of adverse cardiovascular events. However, the risk of death from any cause (febuxostat n=243 (7·8%), allopurinol n=199 (6·4%); HR 1·22 (95% CI 1·01-1·47); p=0·04) and the risk of cardiovascular death (febuxostat n=134 (4·3%), allopurinol n=100 (3·2%); HR 1·34 (95% CI 1·03-1·73); p=0·03) (modified intention to treat analysis) were higher in the febuxostat group than in the allopurinol group in CARES.

Added value of this study

The FAST study was a large, multicentre, prospective, randomised, open-label, blinded endpoint non-inferiority study to compare the cardiovascular safety of febuxostat versus allopurinol in 6128 patients with gout and at least one additional cardiovascular risk factor, who were already treated with allopurinol. The population studied differed from that in the CARES trial. FAST participants were generally at lower cardiovascular risk than CARES participants as only about one third of patients in FAST had prior major cardiovascular comorbidity. Daily doses of febuxostat in FAST were higher (80mg or 120mg daily) than in CARES (40mg or 80 mg daily) and dose ranges of allopurinol were wider in FAST (100mg-900mg daily) than CARES (200-600mg daily). Only 5·8% of patients in FAST withdrew from all follow up, and randomised treatment discontinuation rates (16·5% in the

allopurinol group and 32·4% in the febuxostat group) were lower than in the CARES trial. In CARES, 45·0% of patients did not complete all trial visits and 56·6% of patients discontinued randomised treatment prematurely. FAST used record-linkage to national healthcare databases to complement other methods of reporting for the detection of hospitalisations and deaths. We found that febuxostat was non-inferior to allopurinol for the primary composite endpoint of hospitalisation for non-fatal myocardial infarction/biomarker positive acute coronary syndrome, non-fatal stroke or cardiovascular death during a median on-treatment period of 1324 days [IQR 870, 1919] or 3·63 years. In contrast to CARES, treatment with febuxostat was not associated with an increase in cardiovascular death or all-cause death in FAST, nor in the subgroup of patients in FAST with a baseline history of MI, stroke or acute coronary syndrome. Overall there were fewer deaths in the febuxostat group (62 CV deaths and 108 all-cause deaths (OT), 117 CV deaths and 222 all-cause deaths (ITT)), than in the allopurinol group (82 CV deaths and 174 all-cause deaths (OT), 122 CV deaths and 263 all-cause deaths (ITT)).

Implications of all the available evidence

Whilst the CARES study suggested that febuxostat therapy may be associated with higher risk of all-cause mortality and cardiovascular mortality than allopurinol, the FAST study, with better ascertainment of events, found no increase in these risks.

Introduction

Gout is a metabolic disorder in which prolonged elevation of serum urate can lead to the deposition of crystals of monosodium urate (MSU), tophus formation, chronic inflammatory arthritis, urolithiasis, and nephropathy, as well as to recurrent flares of acute arthritis and bursitis. Gout is frequently associated with co-morbidities such as chronic kidney disease, obesity, diabetes mellitus, hypertension and cardiovascular disease and with increased mortality.[1-3] In addition to treatment of acute flares with anti-inflammatory drugs, management of gout requires long term therapy with urate lowering therapy (ULT) to persistently reduce the SUA below its crystallisation threshold in order to dissolve crystal deposits, prevent further crystal deposition, recurrent flares of gout and progressive joint damage. The most widely used urate lowering medications are the xanthine oxidase inhibitors (XOI), allopurinol and febuxostat. Prophylaxis against acute flares of gout is recommended when treatment is initiated with ULT or following dose increases of a XOI, typically for a period of up to six months.[4]

Initial clinical trials comparing febuxostat to allopurinol or placebo identified a numerically higher risk of cardiovascular events in patients taking febuxostat.[5–8] Marketing authorisation for febuxostat was granted after a subsequent 6-month randomised controlled trial of febuxostat compared to allopurinol in 2269 participants (the CONFIRMS trial)[9] showed equal numbers (0·4%) of adjudicated cardiovascular events with febuxostat 80mg and allopurinol, and no cardiovascular deaths in the febuxostat treated patients. However, because of lingering concerns about the possibility of increased cardiovascular risk with febuxostat, the European Union Risk Management Plan for febuxostat indicated that a post-authorisation safety study should be carried out in Europe in patients with gout to evaluate the cardiovascular effects of febuxostat versus standard urate lowering therapy with allopurinol. The Febuxostat versus Allopurinol Streamlined Trial (FAST) was approved to fulfil this requirement.

Methods

Study Design and participants

A prospective, randomised, open-label, blinded endpoint (PROBE) multi-centre trial was undertaken in patients with gout at 18 regional centres in three countries (UK – Scotland and England, Denmark and Sweden).[10] The study protocol (appendix pp157-217) was approved by ethics committees and regulatory authorities in each country. All participants gave written informed consent.

Patients were mainly recruited from 850 primary care practices in the UK and Denmark (by search of primary care records for potentially eligible patients), but also from two secondary care centres in Scotland, and via two clinical research organisations in Sweden. Eligible patients were aged 60 years or older, with gout,[11] who in the opinion of the recruiting physician required urate lowering therapy. No patients with asymptomatic hyperuricaemia were recruited to the study. Eligible participants had at least one additional cardiovascular risk factor (appendix p6) and were already receiving allopurinol therapy. Patients with a history of myocardial infarction or stroke in the previous 6 months and those with congestive heart failure, New York Heart Association (NYHA) Class III or IV, or severe renal impairment were excluded. A full list of inclusion and exclusion criteria is detailed in the appendix (appendix pp4-5).

Randomisation

At the screening visit, serum urate was measured. If the SUA was not controlled to the European League Against Rheumatism (EULAR) target of < 0·357 mmol/L (<6mg/dL)[12] on the patient's pre-study allopurinol dose, this was increased by 100mg daily every two weeks until the urate was at target or the patient reached the maximum licensed dose (900mg daily) or maximum tolerated dose of allopurinol. This dose increase was carried out because febuxostat 80mg is a more potent urate lowering therapy than low dose allopurinol. The dose increase was carried out every two weeks in all patients who were not yet at target urate, unless there were tolerability issues, or the maximum licensed dose had been reached, in which case patients could continue in the study even if the target urate had not been reached. After the allopurinol dose had been optimised to reach the target urate

level, or immediately for patients who were already controlled to target at screening, patients were randomly allocated to receive allopurinol therapy or febuxostat using a central web-based randomisation facility located at the Robertson Centre for Biostatistics, University of Glasgow. The randomisation system could be accessed via an interactive voice response system or by a web-based application. The randomisation list was created by a statistician in the Robertson Centre based on randomised permuted blocks of size four stratified according to previous cardiovascular events (myocardial infarction, stroke or hospitalisation for congestive heart failure or peripheral vascular disease). Randomised therapy was not blinded to participants, site staff and treating physicians but was blinded to the endpoint adjudication committee.

Post-randomisation, while the majority of patients remained on the daily dose assigned at randomisation, the daily dose of allopurinol or febuxostat could be reduced or increased by a physician within the licensed daily dose limits based on clinical discretion, for example, reduced due to tolerability issues or increased due to inadequate control of urate levels identified during annual visits.

Allopurinol was chosen as the comparator for febuxostat because it is the long-established, first-line ULT for gout.

Procedures

Allopurinol 100mg and 300mg tablets (Salutas Pharma GmbH, Barleben, Germany; Teva Pharmaceutical Works Private Limited company, Debrecen, Hungary) and febuxostat 80mg and 120mg tablets (Patheon France, Bourgoin Jallieu, France; Menarini, Dresden, Germany) were supplied directly by post to participants from the research pharmacy at the University of Dundee (except in Sweden where they were supplied from the Dundee research pharmacy via a local pharmacy). Allopurinol was given orally at the daily dose required to control urate levels to < 0·357 mmol/L or the maximum tolerated or licensed dose. Febuxostat was commenced orally at 80mg daily. After two weeks, the SUA was measured in those taking febuxostat and if not controlled to <

0·357 mmol/L, the febuxostat dose was increased to 120mg daily. All patients had a washout period of seven days (7-21 days) after randomisation before starting randomised therapy.

Six months of prophylaxis against gout flares was offered to all patients at the start of randomised therapy. Prophylaxis was started earlier in any patients whose allopurinol dose was increased during the allopurinol lead-in phase and was offered again at any time during the study when a patient's dose of ULT was increased. First-line gout flare prophylaxis was with colchicine (0·5mg once or twice daily) and second-line alternatives were non-steroidal anti-inflammatory drugs (naproxen, diclofenac or meloxicam) with gastric protection (omeprazole or ranitidine). Patients could decline or discontinue gout flare prophylaxis at any time. Any gout flares that occurred during the study were managed at the discretion of the patient's local treating physician according to local guidelines.

All patients had an annual follow-up visit during which serum urate, urea, creatinine and electrolytes, and liver function tests were measured. In addition, all patients had two-monthly follow-up contacts with the study team. Adverse events could be reported at any time by patients or health professionals. Record-linkage to centralised databases for records of hospitalisations, deaths and cancers was carried out at regular intervals during the study in the UK (Public Health Scotland and NHS Digital) and Denmark (Danish Health Data Board (Sundhedsdatastyrelsen)) (except for the last year of study follow-up in Denmark). Although significant attempts were made by the investigators to obtain similar record-linkage data in Sweden, this was not possible. Because the primary event rates were lower than predicted during the study, the trial recruitment period was extended beyond the two years originally planned and the follow-up period was also extended.

Outcomes

The primary outcome was the composite of: 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) or death due to a cardiovascular event.

The secondary outcomes were: 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 (TIA); hospitalisation for non-fatal cardiac arrest; hospitalisation for venous and peripheral arterial vascular thrombotic event; hospitalisation for arrhythmia with no evidence of ischaemia.

Minor amendments to two components of the primary outcome were made during the trial – hospitalised stroke was amended to include strokes that were non-hospitalised or occurred during a hospitalisation, and myocardial infarction was updated to include myocardial infarction or biomarker positive acute coronary syndrome (which are largely considered to be the same outcome nowadays).

An independent clinical events classification committee based at the University of Glasgow, whose members were unaware of the trial group assignments, assessed all the components of the primary composite outcome, secondary cardiovascular outcomes, and death; these events are defined in the clinical event definitions (appendix pp7-25).

An exploratory efficacy endpoint was also included: the proportion of patients whose serum urate level was < 0·357 mmol/L (<6 mg/dL), and < 0·297 mmol/L (<5 mg/dL) after each year of treatment.

Serious adverse events occurring during and up to 28 days after the end of the study were recorded unless participants had withdrawn consent. Gout flares and any treatment-related adverse events were also recorded.

For adverse events that were potential study endpoints, more detailed information was collected from medical records and death certificates and an anonymised endpoint package was prepared for adjudication by an independent adjudication committee.

Statistical analysis

It was calculated that 456 first primary events were required to show non-inferiority between the febuxostat and allopurinol treatment arms assuming a non-inferiority limit for the hazard ratio of 1·3 with 80% power and a one-sided alpha of 0·025. The non-inferiority margin of 1·3 was selected and approved by the EMA as representing a minimal difference of clinical interest and was based on previous regulatory guidance and precedent. Previous and ongoing cardiovascular safety studies have used similar values which have been accepted by regulators, including cardiovascular safety trials of novel treatments for diabetes, trials comparing celecoxib with other non-steroidal anti-inflammatory drugs and ongoing trials of novel renal treatments[13-17]. With an expected primary event rate of about 10% over three years in the allopurinol group based on events observed in observational databases, it was estimated that 2282 patients would be required in each treatment arm. Assuming a dropout rate of 20% from the on-treatment population, the enrolment of 2853 patients in each treatment arm (5706 total) was predicted to provide the required number of primary events with an average follow-up period of 3 years. Baseline characteristics are shown according to treatment groups as means (SD) or median (IQR) for continuous variables and as numbers and percentages for categorical variables.

All clinical outcomes were analysed on a time to first event basis using Cox proportional hazards models, with the exception of the frequency of flares of gout, for which all recurrent events were counted and analysed using a negative binomial regression model. All analyses were adjusted for the stratification variable and country and the treatment effect for febuxostat relative to allopurinol was estimated, reporting hazard ratios and 95% confidence intervals for the Cox models and incidence rate ratio and 95% confidence interval for the negative binomial model. P-values were calculated from Wald statistics. The primary analysis was an on-treatment (OT) analysis. The OT analyses censored follow-up after permanent discontinuation from original randomised therapy, death from any cause not included in the endpoint being considered, date of withdrawal of all consent to

participate further in the study or end of study (31 December, 2019), whichever occurred first. The intention to treat (ITT) analysis censored follow-up after death from any cause not included in the endpoint being considered, date of withdrawal of all consent to participate further in the study, or end of study, whichever occurred first. In the OT analyses, the primary outcome was assessed first in an OT non-inferiority analysis with a non-inferiority limit of 1·3. A supporting ITT analysis was conducted and, if non-inferiority was demonstrated in this analysis as well as the OT analysis, an ITT superiority analysis was carried out. This hierarchical testing process meant that there was no need for adjustment for multiple testing. Prespecified subgroup analyses were carried out for the primary endpoint. P values for the test of interaction between the variable defining the subgroup and randomised treatment allocation were calculated. Similar analyses were done for other time-to-event secondary endpoints.

Time to event curves are presented as cumulative incidence functions adjusting for the competing risk of deaths not included in the endpoint being plotted.

Between treatment group differences in SUA levels were assessed annually using analysis of covariance, adjusting for baseline levels, the stratification variable, and country.

The type I error rate was set at 2·5% (one-sided) for the one-sided non-inferiority analyses and at 5% for two-sided superiority analyses. No formal interim analyses were carried out and hence no P-value penalties are required. No adjustments were made for the multiplicity of statistical comparisons. Hence, analyses other than for the primary endpoint should be considered exploratory.

All validly randomised participants were included in the OT and ITT analyses. Safety analysis was done for all patients who took at least one dose of randomised medication. The incidence of serious treatment emergent adverse events is summarised by MedDRA system organ class for each treatment group.

Analyses and graphical displays were conducted using SAS for Windows version 9·4 and R version 3·6·1. All cardiovascular outcomes were adjudicated by an independent clinical endpoint committee (appendix p34), except coronary revascularisation, cerebral revascularisation and TIA which were reviewed and classified by physicians at the University of Dundee.

Trial safety was overseen by an independent data monitoring committee (appendix p34). This trial is registered with the EU Clinical Trials Register (EudraCT 2011-001883-23) and ISRCTN (ISRCTN72443728).

Role of the funding source

The study was an investigator-led trial sponsored by the University of Dundee and funded by Menarini. Menarini received support from Ipsen and Teijin Pharma Limited. The funder of the study had no role in study design, data collection, data analysis, data interpretation, writing of the manuscript or the decision to submit. TM, IM, IF and MR had full access to all the data in the study and TM had final responsibility for the decision to submit for publication. The study Clinical Co-ordination Centre was MEMO Research at the University of Dundee and the study Data and Biostatistical Centre was at the Robertson Centre for Biostatistics at the University of Glasgow. Trial monitoring was carried out or subcontracted by the University of Dundee as study sponsor.

Results

From 20 December, 2011, to 17 October, 2017, 6603 patients consented to enrol in the trial and were assessed for eligibility; 475 patients were excluded before randomisation. Data for 14 randomised patients and one non-randomised patient (all recruited at one UK site) were deleted from the study database following instruction by the sponsor because of concerns identified at a monitoring visit regarding the validity of consent and inclusion of these patients and their data. These 15 patients are excluded from all summaries and analyses. A total of 6128 patients were randomly assigned to receive febuxostat (n=3063) or allopurinol (n=3065; figure 1). The final

randomisation took place on 26 January, 2018. Patients stopped randomised treatment at the end of the trial, on 31 December, 2019. The study reached the end of its contracted period on 31 Dec 2019 and the decision to end the trial then was made at a time when the number of adjudicated primary events that had occurred was still uncertain. The final lower than target number of primary events was due to uncertainty about whether some events had occurred 'on treatment' that was later clarified, and a lower than expected number of potential events for which information was still being gathered being adjudicated as positive events. Final record-linkage data and supporting information on endpoints resulted in the trial completion being the end of August 2020. Median follow-up time in the study was 1467 days [IQR 1029-2052] and median on-treatment follow-up period was 1324 days [IQR 870-1919].

The two treatment groups were well balanced with respect to baseline characteristics (table 1) and baseline cardiovascular risk factors (appendix p26), with the exception of a small excess of history of diabetes mellitus (n=719 (23·5%) in the allopurinol group compared to n=661 (21·6%) in the febuxostat group). The mean age was 71·0 years (SD 6·4), 5225 (85·3%) were male and 6070 (99·1%) were white. 38·9% were recruited in Scotland, 27·3% in England, 31·7% in Denmark, and 2·1% in Sweden. 2046 patients (33·4%) had a history of cardiovascular disease (defined as myocardial infarction, cerebrovascular accident, transient ischaemic attack, acute coronary syndrome, coronary revascularisation, angina pectoris or heart failure). 1380 patients (22·5%) had a history of diabetes mellitus.

A total of 3593 patients (58·6%) were taking statins, 2170 patients (35·4%) were taking antiplatelet agents, (including 1828 patients (29·8%) taking aspirin), and 2468 patients (40·3%) were taking an angiotensin-converting enzyme inhibitor at screening.

The median duration of allopurinol therapy at time of screening was 6·0 years [IQR 2·1-14·0]. At the screening visit, most participants were taking 100mg-300mg daily dose of allopurinol (100mg (1951 patients (31·8%)); 200mg (1066 patients (17·4%)); 300mg (2749 patients (44·9%)). In the allopurinol

lead-in phase, 2201 patients (35·9%) required an increase in allopurinol dose to reach EULAR target SUA during the allopurinol lead-in phase. The daily doses of allopurinol taken by participants immediately prior to randomisation are shown in appendix p27. The mean daily dose of allopurinol taken at the end of the lead-in allopurinol up-titration phase was 278mg in the allopurinol group and 274mg in the febuxostat group. At the end of allopurinol up-titration, 97·3% and 96·9% in the allopurinol and febuxostat groups respectively were at target urate. After randomisation, 97·5% of febuxostat daily doses were 80mg and 2·5% were 120mg. For allopurinol daily doses, 10·0% were 100mg, 23·3% were 200mg, 50·9% were 300mg, 11·9% were 400 mg and 3·9% were 500-900 mg. The mean daily dose of febuxostat during the trial was 81mg. The mean daily dose of allopurinol during the trial was 279mg.

In the primary on-treatment analysis, febuxostat therapy was non-inferior to allopurinol therapy for incidence of the primary endpoint (172 patients assigned to febuxostat [1·72 events per 100 patient years]) compared with 241 patients assigned to allopurinol [2·05 events per 100 patient years]); adjusted hazard ratio 0·85 [95% CI 0·70-1·03], p<0·001) (figure 2a). The ITT analysis confirmed non-inferiority of febuxostat (p<0·001) (figure 2b)). Superiority of febuxostat for the primary outcome was not demonstrated (p=0·19). Results obtained in on-treatment and intention to treat analyses for all-cause mortality (figure 3a and b), cardiovascular death (figure 3c and d)), and for the other secondary outcomes are presented in tables 2 and 3. In the on-treatment analysis, the upper limit of the hazard ratio for all-cause mortality was below 1·0. There were 174 deaths (1·44/100 patient years) in the allopurinol group and 108 (1·06/100 patient years) in the febuxostat group, HR (95%CI), 0·75 (0·59, 0·95). In the intention to treat analysis, there were 263 deaths (2·05/100 patient years) in the allopurinol group versus 222 (1·73/100 patient years) in the febuxostat group, HR (95%CI) 0·84 (0·71, 1·01). In contrast there was a nominally significant increase in hospitalisation for arrhythmia with no evidence of ischaemia, with 49 patients (0·385/100 patient years) with an event in the allopurinol group versus 74 patients (0·583/100 patient years) in the febuxostat group.

A total of 28 pre-specified analyses were carried out based on subgroups according to baseline characteristics (appendix pp40-43). Only one subgroup analysis reached statistical significance in the interaction test (on-treatment p=0·001; intention to treat p=0·003). This was for the subgroups defined by pre-randomisation urate levels < 0·297 mmol/L and ≥ 0·297 mmol/L. There was a nominally significant reduction in risk in the febuxostat arm compared to the allopurinol arm in the < 0·297 mmol/L urate subgroup and no statistically significant difference between the two groups in the $\geq$ 0·297 mmol/L subgroup for the primary outcome. The analysis for the primary outcome in the subgroup of patients with a history of MI, stroke or acute coronary syndrome showed no significant difference between treatment groups (allopurinol n=83 (11·8%), febuxostat n=65 (9·5%); adjusted HR 1.02 (95% CI 0·74-1·42); p=0.202 (on treatment analysis). In the intention to treat analysis for this subgroup results were similar (allopurinol n=102 (14·5%), febuxostat n=103 (15·1%); adjusted HR 1·07 (95% CI 0·81-1·41); p=0·119). On the request of a reviewer, an analysis of the composite primary endpoint replacing CV death with all-cause death (on-treatment and intention to treat) and an on-treatment analysis of the same endpoint but extending the on-treatment period by 90 days are presented in the supplementary appendix (pp36-37) The results of these additional analyses were consistent with the main results presented. An on-treatment analysis of the composite outcome of all-cause mortality, non-fatal myocardial infarction/biomarker positive acute coronary syndrome or non-fatal stroke, with additional adjustment for age, sex, low density lipoprotein and high density lipoprotein cholesterol levels, high sensitivity troponin I levels, systolic blood pressure, smoking status and histories (yes/no) of each of diabetes, hypertension and cardiovascular disease is also presented in the supplementary appendix (p38).

There was a greater reduction in urate levels on febuxostat treatment compared to allopurinol treatment. The changes from baseline were compared statistically between the two groups at years 1-7. There were significant differences between the two groups (p<0·0001) in each year with mean differences greater than 0·08 mmol/L for years one to six. After randomisation, 1044 patients in the allopurinol arm experienced at least one gout flare compared to 1017 patients in the febuxostat

arm. The rates of gout flares were 19·85 gout flares/100 patient years for allopurinol and 17·95 gout flares/100 patient years for febuxostat.

A total of 3050 patients in the allopurinol group and 3001 patients in the febuxostat group took at least one dose of randomised study medication and were included in the safety population (n=6051). In the febuxostat group, 973 patients [32·4%] discontinued randomised therapy compared with 503 patients [16·5%] on allopurinol. The excess withdrawals and withdrawals from treatment in the febuxostat arm occurred in the first year of follow-up, with most occurring in the first six months (appendix pp38-39). Colchicine was the most commonly dispensed gout flare prophylaxis and was dispensed to 1603 patients in the allopurinol group and 2223 patients in the febuxostat group (appendix p28).

A total of 263 (8·6%) patients died and 1812 (59·4%) experienced at least one serious adverse event in the allopurinol group compared to 222 (7·2%) and 1720 (57·3%) in the febuxostat group (Table 4 and appendix p30, p32). Differences were seen in the incidence of endocrine disorders, and neoplasms (benign, malignant and unspecified (including cysts and polyps)) between treatment groups. The upper limit of normal for creatinine was 106 µmol/L in males and 80 µmol/L in females. 31% of patients had at least one value above this limit in the allopurinol group and 34% in the febuxostat group. Only 24 patients had serious adverse events that were considered treatment-related, 19 in the febuxostat group and 5 in the allopurinol group. There were 28 treatment-related serious adverse events in total. The most obvious difference between treatment groups for treatment-related serious adverse events was for gastrointestinal disorders (8 for the febuxostat group versus 1 for the allopurinol group). In the allopurinol group, the five treatment-related serious adverse events were angina (two cases), thrombocytopenia, dyspepsia and arthralgia (all recovered). In the febuxostat group, the 23 treatment-related serious adverse events in 19 patients were pancreatitis (five episodes in four patients; one patient recovered, two recovered with sequelae; one patient had pancreatitis that recovered, then had a further episode of pancreatitis with

gastrointestinal perforation, circulatory collapse and death), diarrhoea (three cases, all recovered, one additionally associated with acute renal failure which recovered), atrial fibrillation (three cases, two recovered, one not recovered), cholecystitis (two cases, one recovered, one recovered with sequelae). The other treatment-related serious adverse events in the febuxostat group were single cases of haematuria and non-cardiac chest pain (recovered), and worsening renal failure, abnormal liver function tests, rotator cuff syndrome and pneumonia (recovered with sequelae). Because all patients were taking allopurinol at baseline, those randomised to the allopurinol group were inherently less likely to experience treatment-related serious adverse events during the trial, than those allocated to the febuxostat group (a novel treatment). More patients overall were reported to be suffering from a malignant neoplasm in the allopurinol arm 384 (12·6%) versus 322 (10·7%) in the febuxostat arm (appendix p31). In the 28 day period following the end of the study, four deaths were reported in each treatment group.

Discussion

This FAST study has clearly demonstrated that in more than 6000 patients with gout receiving ULT with a xanthine oxidase inhibitor at doses designed to lower the urate to EULAR target levels <0.357mmol/L for up to seven years, febuxostat was non-inferior to allopurinol with regard to the occurrence of major cardiovascular outcomes comprising the primary outcome of hospitalisation for non-fatal myocardial infarction/biomarker positive acute coronary syndrome, non-fatal stroke or death due to a cardiovascular event. This was demonstrated in both the primary on-treatment and intention to treat analyses. Importantly, there was no signal of increased mortality, with a lower rate of all-cause deaths and cardiovascular deaths reported in the febuxostat group than in the allopurinol group. This contrasts with the findings of the North American Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout trial (CARES) which reported that in patients with gout and established cardiovascular comorbidities at baseline, while febuxostat was non-inferior to allopurinol with respect to rates of the primary endpoint of the study (a composite of death from cardiovascular causes, myocardial infarction, stroke, or unstable angina with urgent

revascularisation), the rates of the secondary outcomes of adverse cardiovascular outcomes, all-cause death and cardiovascular death were significantly higher with febuxostat than with allopurinol.[17] However, when efforts were made to trace patients in CARES lost to follow-up, this mortality difference was no longer seen, and it was unclear why increased mortality was associated with lower doses of febuxostat. This could simply have been information bias caused by the inability to adequately follow up those who withdrew from CARES. The supporting analyses of CARES where private investigators followed up the vital status of those who withdrew found that the signal of increased mortality was no longer significant and supports this view.

Although of similar size, there are several differences between the CARES trial and the FAST trial. All patients in CARES had established cardiovascular disease, while only 33% of patients in FAST had cardiovascular disease at baseline. CARES included patients with severe heart failure who might have particularly poor cardiovascular prognosis, whereas FAST excluded patients with NYHA III or IV heart failure. The prevalence of tophi was greater in the CARES population, suggesting more severe gout at baseline. CARES allowed inclusion of newly treated patients, while FAST only recruited patients who were already established on allopurinol therapy and may therefore have had a lower urate crystal burden, which might be important for cardiovascular risk. To what extent the results of FAST are generalisable to patients with gout who have not previously been treated with ULT, or to patients with severe heart failure is not clear. The doses of randomised medication were different in the two trials, with a lower dose of febuxostat being used in CARES (40-80mg daily) compared with FAST (80mg-120mg daily) and the range of doses of allopurinol differed (200-600mg daily in CARES; 100-900mg daily in FAST), reflecting the different dose ranges for the two XOIs approved by regulatory agencies in North America and Europe. In the CARES trial, 56·6% of patients discontinued randomised treatment prematurely and 45·0% of patients withdrew and did not complete all trial visits and were therefore not followed up until the end of the trial. In the FAST study, there were lower rates of treatment discontinuation (16·5% in the allopurinol group and 32·4% in the febuxostat

group) and much better rates of patient follow up with only 5·8% of patients in FAST withdrawing from all follow up.

The results of the CARES study led to regulators issuing alerts from 2017 onwards and subsequently changing prescribing advice for febuxostat and recommending that treatment with febuxostat should be avoided in patients with pre-existing major cardiovascular diseases (e.g. myocardial infarction, stroke or unstable angina), unless no other therapeutic options are appropriate. At the time this advice was released in Europe and the UK, the Medicines and Healthcare Regulatory Agency (MHRA) requested that the FAST investigators should provide an updated risk-benefit assessment about whether the study should continue. An independent risk-benefit assessment led to the MHRA making the recommendation in 2018 that FAST should continue unchanged. However, it is likely that the regulatory advice released to healthcare professionals at this time may have increased withdrawals from randomised medication in the febuxostat arm of the study. Notably, no increased risk of adverse cardiovascular events was found in the FAST subgroup of patients with prior MI, stroke or acute coronary syndrome, who were very similar to the patients included in the CARES study.

The FAST study finished underpowered for the required number of primary events, with 413 events instead of the planned target of 456 events. The lower number of primary events will have resulted in only a modest reduction in statistical power from 80% to approximately 77% to exclude a non-inferiority limit of 1·3, or alternatively, 80% power to exclude a non-inferiority limit of 1·315.

The primary analysis of FAST, endorsed by the EMA, was an on-treatment rather than intention-to-treat analysis, as is commonly the case in a non-inferiority safety trial. In such trials, on-treatment analysis results in a comparison that is undiluted by periods when the medications under investigation were not taken. In FAST, our research pharmacy had regular contact with all trial participants about adherence so our ascertainment of exposure to randomised medications was good. However, an on-treatment analysis may not provide a true unbiased analysis of the

randomised population if there are differential discontinuation rates, as indeed there were in FAST, with higher discontinuation rates and earlier discontinuations of febuxostat than allopurinol. This could have been influenced by the higher use of colchicine in patients randomised to febuxostat and the fact that switching from any established drug therapy to a new drug therapy usually results in more discontinuations in trials. For this reason, a supporting ITT analysis was also done. Because we were able to follow up patients until the end of the trial by telephone and other personal contact and by record-linkage to national hospitalisation and death records (except for the small proportion who withdrew completely), our ascertainment of outcomes in the ITT analysis was very good. Both analyses provided similar mortality findings.

Although an association between serum urate concentrations and cardiovascular disease is well established from numerous observational studies the hypothesis that hyperuricaemia has a direct causal role in the aetiopathogenesis of comorbid cardiovascular disease remains controversial and is not supported by Mendelian randomisation studies.[18,19]

Colchicine use was greater in the febuxostat group, probably because more patients switching therapy to febuxostat chose to accept gout flare prophylaxis than those continuing on allopurinol. Although some recent trials have demonstrated that treatment with colchicine improved outcomes in patients with recent myocardial infarction, and chronic coronary disease, published evidence that treatment with colchicine may be associated with improvements in cardiovascular outcomes has been inconsistent.[20-23] In FAST, while prophylaxis against flares of gout was offered to all patients, only some accepted it, those who took it mainly did so at the very beginning of the trial, and it is likely that some patients chose to take it for less than the six months provided. It is unlikely that the relatively short-term administration of low dose colchicine or NSAIDs as prophylaxis, or any differences in concomitant use of colchicine or NSAIDs, even with the imbalances between treatment groups, had any major effect on the long-term outcomes of FAST. A new figure has been

added to the supplementary appendix (Figure S5, pp50-51) to show the effects of prophylaxis or concomitant use of NSAIDs or colchicine.

As neither the FAST nor CARES trial had a placebo arm for comparison against active treatment with XOI, it is possible that either or both XOIs may actually protect patients with gout against cardiovascular disease and mortality. Certainly, the cardiovascular event rates in the FAST study were lower than anticipated. A large randomised trial comparing allopurinol 600mg daily therapy versus usual care, the ALL-HEART study,[24] is currently underway in the UK to determine if allopurinol has a beneficial effect on major cardiovascular outcomes in patients with ischaemic heart disease (IHD). Should allopurinol be of benefit in IHD, a case could be made to carry out a randomised trial of febuxostat vs usual care or placebo in patients with cardiovascular disease.

Other findings of FAST may deserve further research. One possibility is to investigate the findings of numerically higher non-CV deaths and malignancies with allopurinol than febuxostat. Another is to investigate the higher rate of hospitalisations for arrhythmias without evidence of ischaemia found in FAST.

In summary, we found that febuxostat 80-120mg was non-inferior to allopurinol 100-900mg with respect to its impact on adverse cardiovascular events. In contrast to a previous large study, we found no signal of increased all-cause or cardiovascular mortality with febuxostat. In the light of these findings, regulatory advice to avoid the use of febuxostat in patients with cardiovascular disease should be reconsidered and modified.

Contributors

The idea for the study was conceived by TM. TM, IF and GN formed the Executive Committee of the trial. TM, IF, GN and IM participated in the design of the study. MR and IF did the statistical analysis. IM wrote the first draft of the manuscript with input from IF and TM. All authors participated in the

interpretation of the data, and critical review of the manuscript. All authors have read and approved the final version.

Declaration of interests

IM reports research grants from Novartis, NIHR HTA, Amgen, RTI, Tenovus Scotland, George Clinical, EMA, Sanofi, HDR UK and IMI outside the submitted work and from Menarini for the submitted work and personal income from AstraZeneca outside the submitted work. IF and MR report grants from Menarini via University of Dundee for the submitted work. GN reports grants from Menarini via University of Dundee for the submitted work. JH reports grants from Astellas, Pfizer, Almirall, Servier, Leo Pharma and Novo Nordisk, outside of the submitted work. MW reports personal fees from Portola Pharmaceuticals and Myokardia Inc outside of the submitted work. RDC reports grants and personal fees from Bayer, Boehringer Ingelheim, BMS/Pfizer, Daiichi Sankyo, AstraZeneca, Menarini and Novartis, outside the submitted work. FPR reports speaker/advisory/educational fees from Astellas, Grünenthal, Horizon, Menarini, Syneos, Springer, Wolters-Kluwer, Spanish Foundation of Rheumatology; Investigation funds from Cruces Rheumatology Association. Member of the Pharmacy Corporative Commission of the Basque Health Service. JM reports payments to my employer, Glasgow University, for my work on clinical trials, consulting and other activities: Alnylam, Amgen, AstraZeneca, Bayer, BMS, Cardurion, Cytokinetics, Dal-Cor, GSK, Novartis, Pfizer, Theracos and personal lecture fees from: Abbott, Hickma, Sun Pharmaceuticals, Servier. TM reports grants from Novartis, Pfizer, GSK, Amgen outside the submitted work and from Menarini for the submitted work and personal income for consultancy or speaker fees from Novartis, Takeda, Servier, Shire, Astellus, Menarini and AstraZeneca. CH, JW, SR and EF declare no competing interests.

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References

1 Hansildaar R, Vedder D, Baniaamam M, Tausche AK, Gerritsen M, Nurmohamed MT. Cardiovascular risk in inflammatory arthritis: rheumatoid arthritis and gout [published online ahead of print, 2020 Sep 1]. Lancet Rheumatol. 2020;10.1016/S2665-9913(20)30221-6.

2 Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007-2008. Am J Med. 2012; 125: 679-87.

3 Richette P, Clerson P, Perissin L, Flipo RM, Bardin T. Revisiting comorbidities in gout: a cluster analysis. Ann Rheum Dis 2015; 74: 142-7.)

4 Hui M, Carr A, Cameron S, et al. The British Society for Rheumatology Guideline for the Management of Gout. Rheumatology (Oxford). 2017 Jul 1;56(7):1056-1059.

5 Becker MA, Schumacher HR Jr, Wortmann RL, et al. Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase: a twenty-eight-day, multicenter, phase II, randomized, double-blind, placebo-controlled, dose-response clinical trial examining safety and efficacy in patients with gout. Arthritis Rheum. 2005;52(3):916-923.

6 Schumacher HR Jr, Becker MA, Wortmann RL, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. Arthritis Rheum. 2008;59(11):1540-1548.

7 Schumacher HR Jr, Becker MA, Lloyd E, MacDonald PA, Lademacher C. Febuxostat in the treatment of gout: 5-yr findings of the FOCUS efficacy and safety study. Rheumatology (Oxford). 2009;48(2):188-194.

8 Becker MA, Schumacher HR, MacDonald PA, Lloyd E, Lademacher C. Clinical efficacy and safety of successful longterm urate lowering with febuxostat or allopurinol in subjects with gout. J Rheumatol. 2009; 36:1273–82.

9 Becker MA, Schumacher HR, Espinoza LR, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. Arthritis Res Ther. 2010; 12:R63.

10 MacDonald TM, Ford I, Nuki G, et al. 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. BMJ Open. 2014;4(7):e005354.

11 Taylor WJ, Fransen J, Jensen TL et al. Study for Updated Gout Classification Criteria: Identification of Features to Classify Gout. Arthritis Care Res (Hoboken)2015; 67(9): 1304-15.

12 Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis. 2017;76(1):29-42.

13 Cefalu WT, Kaul S, Gerstein HC, et al. Cardiovascular Outcomes Trials in Type 2 Diabetes: Where Do We Go From Here? Reflections From a Diabetes Care Editors' Expert Forum. Diabetes Care. 2018;41(1):14-31.

14 FibroGen Announces Positive Phase 3 Pooled Roxadustat Safety and Efficacy Results for Treatment of Anemia in Chronic Kidney Disease. https://investor.fibrogen.com/news-releases/news-

release-details/fibrogen-announces-positive-phase-3-pooled-roxadustat-safety-and (Accessed online 16.10.2020)

15 Bohula EA, Wiviott SD, McGuire DK, et al. Cardiovascular safety of lorcaserin in overweight or obese patients. N Engl J Med 2018 Sep 20;379(12):1107-1117. Doi: 10.1056/NEJMoa1808721. Epub 2018 Aug 26.

16 Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. N Engl J Med. 2016 Dec 29;375(26):2519-29. Doi: 10.1056/NEJMoa1611593. Epub 2016 Nov 13.

17 White WB, Saag KG, Becker MA, et al. Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout. N Engl J Med. 2018;378(13):1200-1210.

18 Li X, Meng X, Timofeva M et al. Serum uric acid levels and multiple health outcomes: umbrella review of evidence from observational studies, randomised controlled trials and Mendelian randomisation studies. BMJ 2017; 357: j2376.

19 White J, Sofat R, Hemani G, et al. Plasma urate concentration and risk of coronary heart disease: a Mendelian randomisation analysis. Lancet Diabetes Endocrinol. 2016;4(4):327-336.

20 Bouabdallaoui N, Tardif J-C, Waters DD, et al. Time-to-treatment initiation of colchicine and cardiovascular outcomes after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT). Eur Heart J 2020 Aug 29;ehaa659. Doi:10.1093/eurheartj/ehaa659. (online ahead of print).

21 Al-Abdouh A, Barbarawi M, Khan SU, et al. Colchicine therapy in patients with coronary artery disease: a systematic review and meta-analysis of randomized controlled trials. Coron Artery Dis 2020 Jul 23. Doi: 10.1097/MCA.0000000000000931 (online ahead of print).

22 Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in patients with chronic coronary disease. N Engl J Med. 2020 Aug 31. doi: 10.1056/NEJMoa2021372 (online ahead of print).

23 Tardif J-C, Kouz S, Waters DD, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. N Engl J Med. 2019 Dec 26;381(26):2497-2505. doi: 10.1056/NEJMoa1912388. Epub 2019 Nov 16.

24 Mackenzie IS, Ford I, Walker A, et al. Multicentre, prospective, randomised, open-label, blinded end point trial of the efficacy of allopurinol therapy in improving cardiovascular outcomes in patients with ischaemic heart disease: protocol of the ALL-HEART study. BMJ Open. 2016;6(9):e013774.