82e CONGRÈS

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SOCIÉTÉ DE RHUMATOLOGIE DE L'OUEST

Actualités 2019

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Arthrose :

- Nouvelle saison de la Saga Tanezumab !
- Les biothérapies ou DMARDs dans le traitement de l'arthrose digitale ?

Goutte :

- Brève d'un All-Black !
- Infirmière de pratique avancée… une solution pour le goutteux !
- Febuxostat : tout n'est pas blanc, tout n'est pas noir !

Clinical and epidemiological research

EXTENDED REPORT

Efficacy and safety of tanezumab monotherapy or combined with non-steroidal anti-inflammatory drugs in the treatment of knee or hip osteoarthritis pain

Thomas J Schnitzer,[1] Evan F Ekman,[2] Egilius L H Spierings,[3] H Scott Greenberg,[4] Michael D Smith,[4] Mark T Brown,[4] Christine R West,[4] Kenneth M Verburg[4]

Handling editor Tore K Kvien

► Additional material is published online. To view please visit the journal (http://dx.doi.org/10.1136/annrheumdis-2013-204905).

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Received 12 November 2013
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ABSTRACT

Objective To evaluate whether subjects with knee or hip osteoarthritis (OA) pain on non-steroidal anti-inflammatory drugs (NSAIDs) received greater benefit when tanezumab monotherapy replaced or was coadministered with NSAIDs.

Methods Subjects (N=2700) received intravenous tanezumab (5 or 10 mg) or placebo every 8 weeks with or without oral naproxen 500 mg twice daily or celecoxib 100 mg twice daily. Efficacy was assessed as change from baseline to week 16 in three co-primary endpoints: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain, WOMAC Physical Function and Patient's Global Assessment (PGA) of OA. Safety assessments included adverse events, physical and neurological examinations, laboratory tests and vital signs.

Results Although all tanezumab treatments provided significant improvements in WOMAC Pain and Physical Function over either NSAID alone, only tanezumab +NSAIDs were significant versus NSAIDs with PGA and met the prespecified definition of superiority. Combination treatment did not substantially improve pain or function over tanezumab monotherapy. Adverse event frequency was higher with tanezumab than with NSAIDs and highest with combination therapy. Higher incidence of all-cause total joint replacements occurred with tanezumab+NSAID versus tanezumab monotherapy or NSAIDs. Rapidly progressive OA incidence was significantly greater versus NSAID in all tanezumab groups except tanezumab 5 mg monotherapy.

Conclusions Subjects receiving partial symptomatic relief of OA pain with NSAIDs may receive greater benefit with tanezumab monotherapy. While only coadministration of tanezumab with NSAIDs met the definition of superiority, combination treatment did not provide important benefits over tanezumab monotherapy; small differences in efficacy were negated by treatment-limiting or irreversible safety outcomes.

Trial registration number NCT00809354

To cite: Schnitzer TJ, Ekman EF, Spierings ELH, *et al*. *Ann Rheum Dis* Published Online First: [please include Day Month Year] doi:10.1136/annrheumdis-2013-204905

INTRODUCTION

Tanezumab is a humanised monoclonal antibody with high affinity and selectivity for the pain-mediating neurotrophin nerve growth factor (NGF).[1–3] Efficacy of this compound in relieving chronic pain appears promising.[3–10] In clinical trials of subjects with osteoarthritis (OA) pain, tanezumab consistently improved pain, function and patient global assessments of disease activity versus placebo or naproxen treatment.[1–3 6 7] Recently, we reported that tanezumab added to a stable diclofenac sustained release regimen provided significantly greater efficacy than diclofenac plus placebo but was associated with higher adverse event incidence.[11]

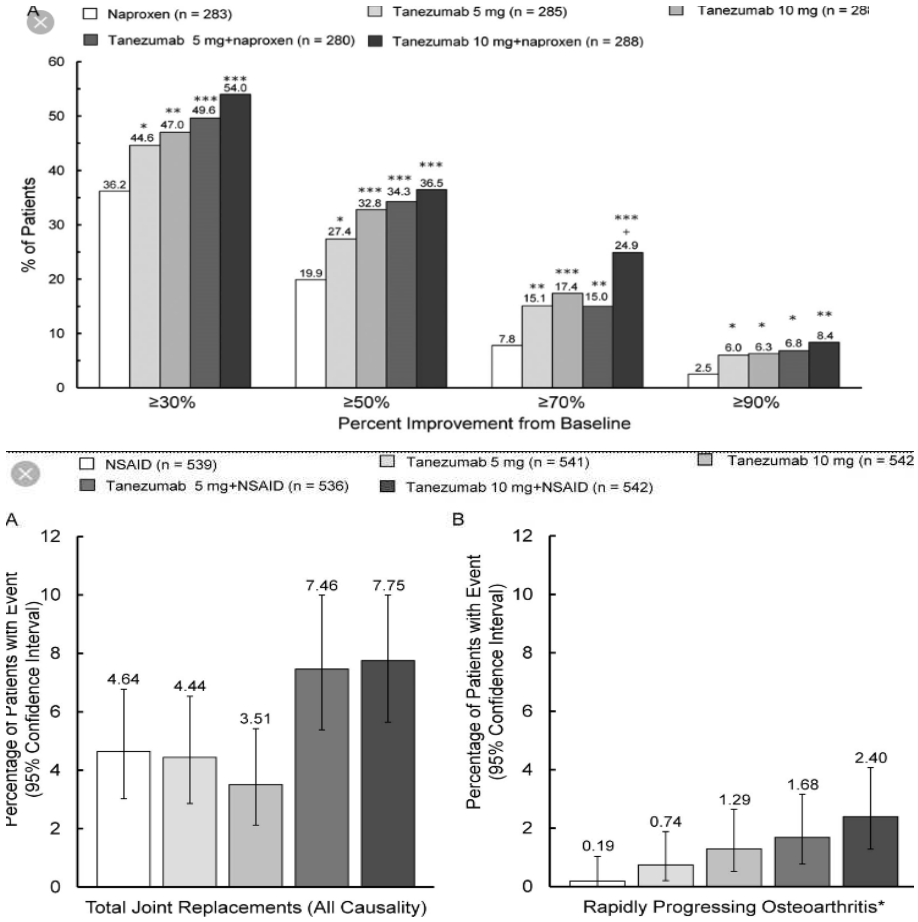
To extend results of prior tanezumab studies, we examined efficacy and safety of tanezumab administered either alone (monotherapy) or in combination with a non-steroidal anti-inflammatory drug (NSAID; naproxen 500 mg twice daily or celecoxib 100 mg twice daily) versus NSAID alone for treatment of OA pain. The objectives of this study were to determine (1) whether subjects receiving only partial symptomatic relief of OA pain on a stable naproxen or celecoxib regimen received greater benefit after switching to tanezumab and (2) whether addition of tanezumab to a stable NSAID regimen provided additional benefit. This study differs from previous studies in the choice of active comparators and the study design that allows evaluation of tanezumab monotherapy and tanezumab +NSAIDs simultaneously.

METHODS

This was a double-blind, parallel-group, multicentre, randomised clinical trial of subjects with OA pain of the knee or hip receiving only partial pain relief from a stable naproxen or celecoxib regimen but otherwise tolerating treatment. The study was conducted in compliance with the Declaration of Helsinki and all International Conference on Harmonisation Good Clinical Practice guidelines and registered at clinicaltrials.gov (NCT00809354). The protocol and informed consent documentation were reviewed and approved by Institutional Review Boards or Ethics Committees. Subjects provided written informed consent before protocol-specified procedure initiation.

Study population

Eligible subjects were 18 years of age or older, had a diagnosis of knee or hip OA based on American College of Rheumatology criteria with radiographic confirmation (Kellgren-Lawrence grade ≥2 on a scale of 0–4),[12 13] body mass index ≤ 39 kg/m^2, taking stable oral NSAID (naproxen (500–1000



Schnitzer TJ. Ann Rheum Dis. 2015;74(6):1202-11.

When Is Osteonecrosis Not Osteonecrosis?

Adjudication of Reported Serious Adverse Joint Events in the Tanezumab Clinical Development Program

Marc C. Hochberg,[1] Leslie A. Tive,[2] Steven B. Abramson,[3] Eric Vignon,[4] Kenneth M. Verburg,[5] Christine R. West,[5] Michael D. Smith,[5] and David S. Hungerford[6]

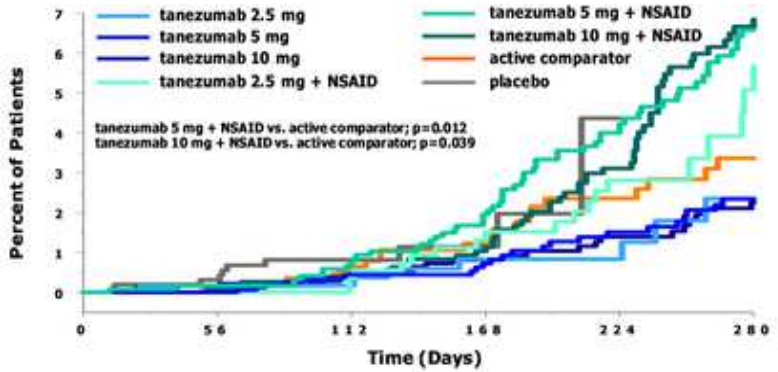
Objective. Tanezumab, a monoclonal antibody against nerve growth factor, has demonstrated efficacy in clinical trials of chronic pain in osteoarthritis (OA) and chronic low back pain. Unexpected adverse events (AEs) described as osteonecrosis (ON) occurred during tanezumab development, leading the US Food and Drug Administration to impose a partial clinical hold for all indications except cancer pain. A blinded Adjudication Committee (AC) including orthopedic surgeons, rheumatologists, and an orthopedic pathologist reviewed and adjudicated joint-related AEs in the tanezumab clinical program.

Methods. The AC adjudicated all reported cases of ON as well as cases of total joint replacements (TJRs) not reported as ON for which radiographs obtained within 9 months of the surgery were available. The AC prespecified categories for joint safety events including primary ON, worsening OA (rapid progression of OA [RPOA], normal progression of OA, insufficient information to distinguish between rapid and normal progression of OA), other, or insufficient information to distinguish between primary ON and worsening OA or another diagnosis.

Results. The AC reviewed events in 249 of 386 patients with an investigator-reported AE of ON and/or a TJR. Two events were adjudicated as primary ON, 200 events were adjudicated as worsening OA (68 of which were classified as RPOA), 29 events had another diagnosis, 11 had insufficient information to distinguish primary ON from worsening OA, and 7 did not have committee member consensus.

Conclusion. Despite initial reports, tanezumab treatment was not associated with an increase in ON but was associated with an increase in RPOA. Higher doses of tanezumab, tanezumab administered with nonsteroidal antiinflammatory drugs, and preexisting subchondral insufficiency fractures were risk factors for RPOA in this cohort.

Tanezumab, a humanized monoclonal antibody, specifically targets and inhibits, with high affinity, interaction of nerve growth factor (NGF) with its receptors, TrkA (neurotrophic tyrosine kinase receptor type 1) and p75 (a low-affinity NGF receptor) (1–11). Tanezumab has been shown to reduce pain and improve function and patient's global assessment in patients with osteoarthritis (OA) of the knee and hip and those with chronic low back pain in phase II and III randomized controlled clini-



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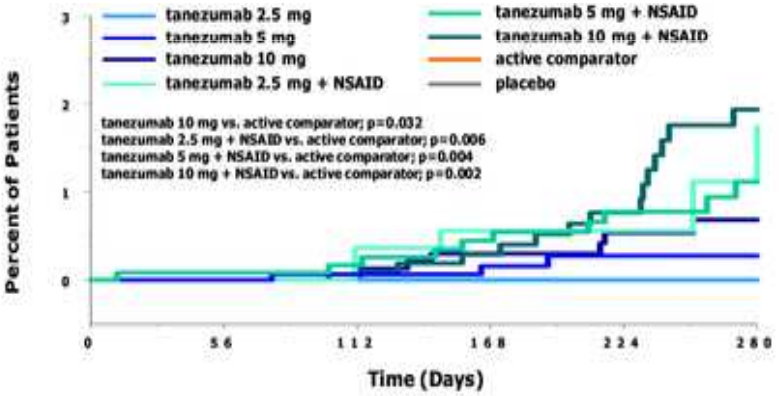
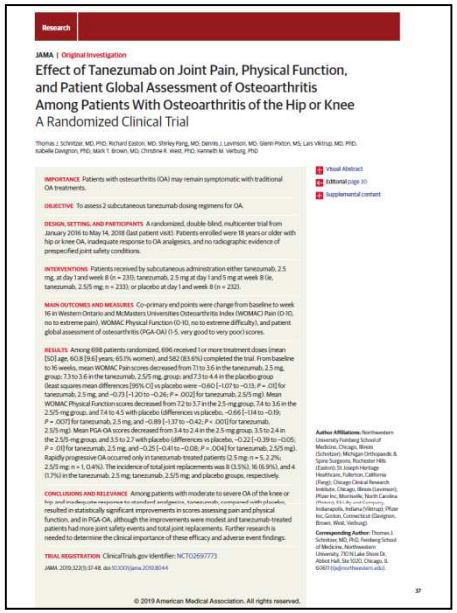


Ostéonécrose

Hochberg MC. Arthritis Rheum. 2016;68(2):985-90.



Research

JAMA | Original Investigation

Effect of Tanezumab on Joint Pain, Physical Function, and Patient Global Assessment of Osteoarthritis Among Patients With Osteoarthritis of the Hip or Knee

A Randomized Clinical Trial

Thomas J. Schnitzer, MD, PhD; Richard Easton, MD; Shirley Pang, MD; Dennis J. Levinson, MD; Glenn Pixton, MS; Lars Viktrup, MD, PhD; Isabelle Davignon, PhD; Mark T. Brown, MD; Christine R. West, PhD; Kenneth M. Verburg, PhD

IMPORTANCE Patients with osteoarthritis (OA) may remain symptomatic with traditional OA treatments.

OBJECTIVE To assess 2 subcutaneous tanezumab dosing regimens for OA.

DESIGN, SETTING, AND PARTICIPANTS A randomized, double-blind, multicenter trial from January 2016 to May 14, 2018 (last patient visit). Patients enrolled were 18 years or older with hip or knee OA, inadequate response to OA analgesics, and no radiographic evidence of prespecified joint safety conditions.

INTERVENTIONS Patients received by subcutaneous administration either tanezumab, 2.5 mg, at day 1 and week 8 (n = 233); tanezumab, 2.5 mg at day 1 and 5 mg at week 8 (ie, tanezumab, 2.5/5 mg, n = 233); or placebo at day 1 and week 8 (n = 232).

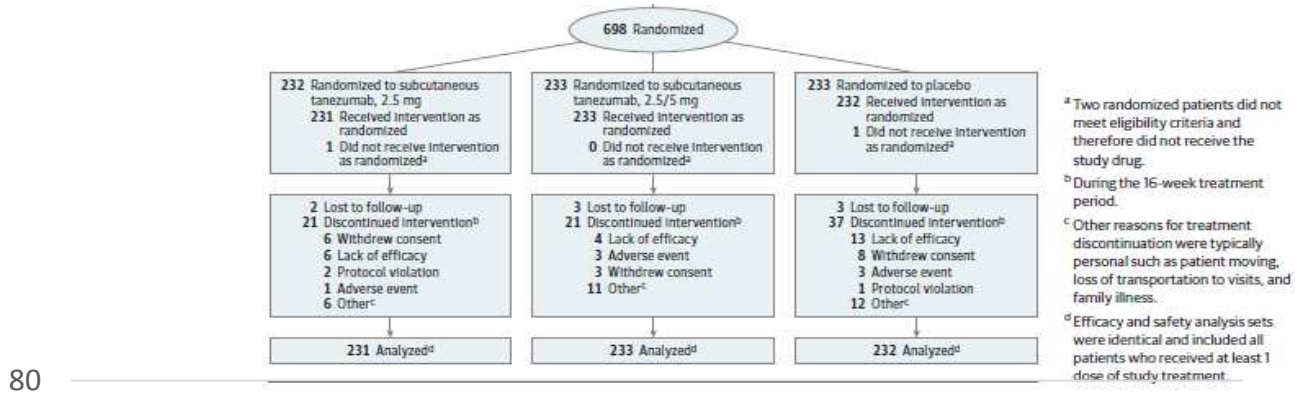
MAIN OUTCOMES AND MEASURES Co-primary end points were change from baseline to week 16 in Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC) Pain (0-10, no to extreme pain), WOMAC Physical Function (0-10, no to extreme difficulty), and patient global assessment of osteoarthritis (PGA-OA) (1-5, very good to very poor) scores.

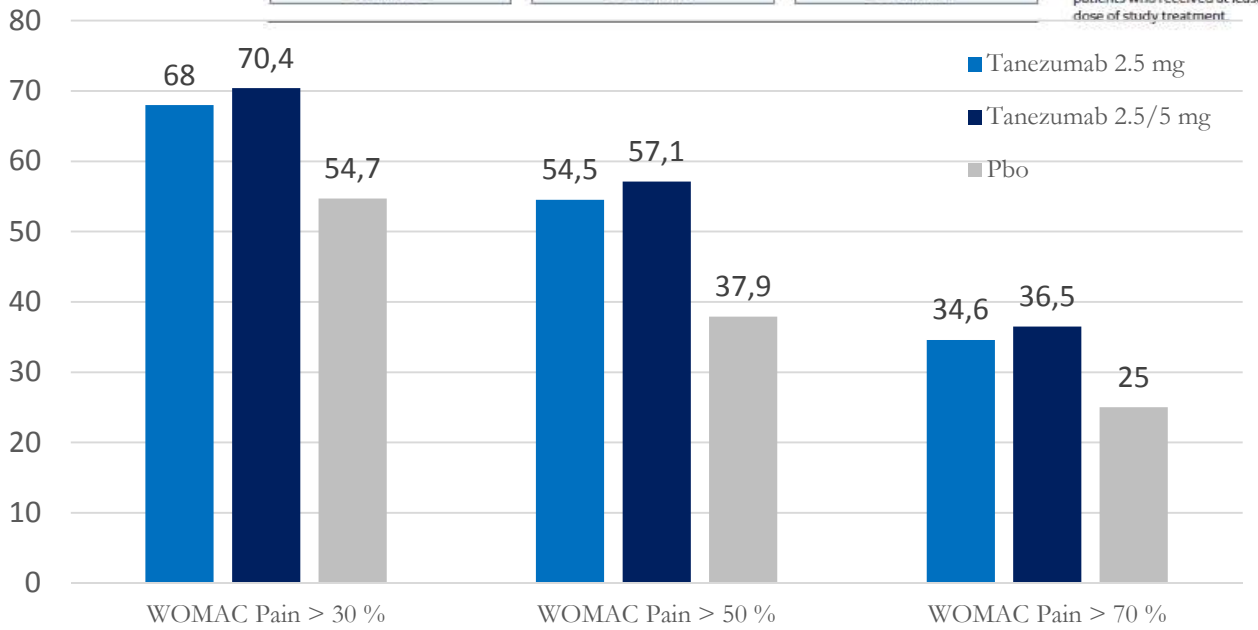
RESULTS Among 698 patients randomized, 696 received 1 or more treatment doses (mean [SD] age, 60.8 [9.8] years; 65.1% women), and 582 (83.6%) completed the trial. From baseline to 16 weeks, mean WOMAC Pain scores decreased from 7.1 to 3.6 in the tanezumab, 2.5 mg, group; 7.3 to 3.6 in the tanezumab, 2.5/5 mg, group; and 7.3 to 4.4 in the placebo group (least squares mean differences [95% CI] vs placebo were −0.60 [−1.07 to −0.13; $P = .01$] for tanezumab, 2.5 mg; and −0.75 [−1.20 to −0.29; $P = .002$] for tanezumab, 2.5/5 mg). Mean WOMAC Physical Function scores decreased from 7.2 to 3.7 in the 2.5-mg group, 7.4 to 3.6 in the 2.5/5-mg group, and 7.4 to 4.5 with placebo (differences vs placebo, −0.66 [−1.14 to −0.19; $P = .007$] for tanezumab, 2.5 mg, and −0.89 [−1.37 to −0.42; $P < .001$] for tanezumab, 2.5/5 mg). Mean PGA-OA scores decreased from 3.4 to 2.4 in the 2.5-mg group, 3.5 to 2.4 in the 2.5/5-mg group, and 3.5 to 2.7 with placebo (differences vs placebo, −0.22 [−0.39 to −0.05; $P = .01$] for tanezumab, 2.5 mg, and −0.25 [−0.41 to −0.08; $P = .004$] for tanezumab, 2.5/5 mg). Rapidly progressive OA occurred only in tanezumab-treated patients (2.5 mg: n = 5, 2.2%; 2.5/5 mg: n = 1, 0.4%). The incidence of total joint replacements was 8 (3.5%), 16 (6.9%), and 4 (1.7%) in the tanezumab, 2.5 mg; tanezumab, 2.5/5 mg; and placebo groups, respectively.

CONCLUSIONS AND RELEVANCE Among patients with moderate to severe OA of the knee or hip and inadequate response to standard analgesics, tanezumab, compared with placebo, resulted in statistically significant improvements in scores assessing pain and physical function, and in PGA-OA, although the improvements were modest and tanezumab-treated patients had more joint safety events and total joint replacements. Further research is needed to determine the clinical importance of these efficacy and adverse event findings.

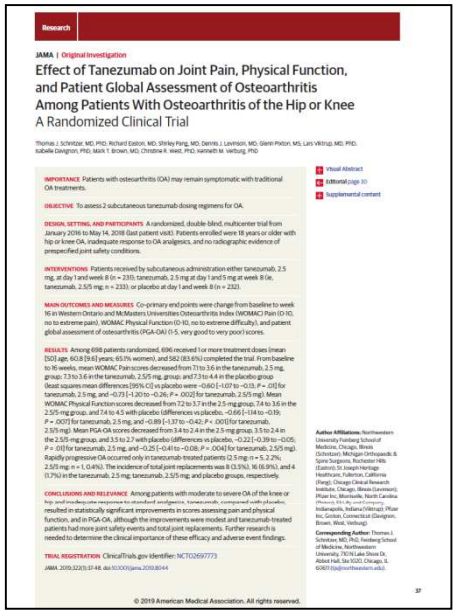
TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02697773

JAMA. 2019;322(1):37-48. doi:10.1001/jama.2019.8044





Schnitzer TJ. JAMA. 2019;322(1):37-48.



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TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02697773

JAMA. 2019;322(1):37-48. doi:10.1001/jama.2019.8044

Visual Abstract

Editorial page 30

Supplemental content

Author Affiliations: Northwestern University Feinberg School of Medicine, Chicago, Illinois (Schnitzer); Michigan Orthopaedic & Spine Surgeons, Rochester Hills (Easton); St. Joseph Heritage Healthcare, Fullerton, California (Pang); Chicago Clinical Research Institute, Chicago, Illinois (Levinson); Pfizer Inc, Morrisville, North Carolina (Pixton); Eli Lilly and Company, Indianapolis, Indiana (Viktrup); Pfizer Inc, Groton, Connecticut (Davignon, Brown, West, Verburg).

Corresponding Author: Thomas J. Schnitzer, MD, PhD, Feinberg School of Medicine, Northwestern University, 710 N Lake Shore Dr, Abbot Hall, Ste 3020, Chicago, IL 60611 (tjs@northwestern.edu).

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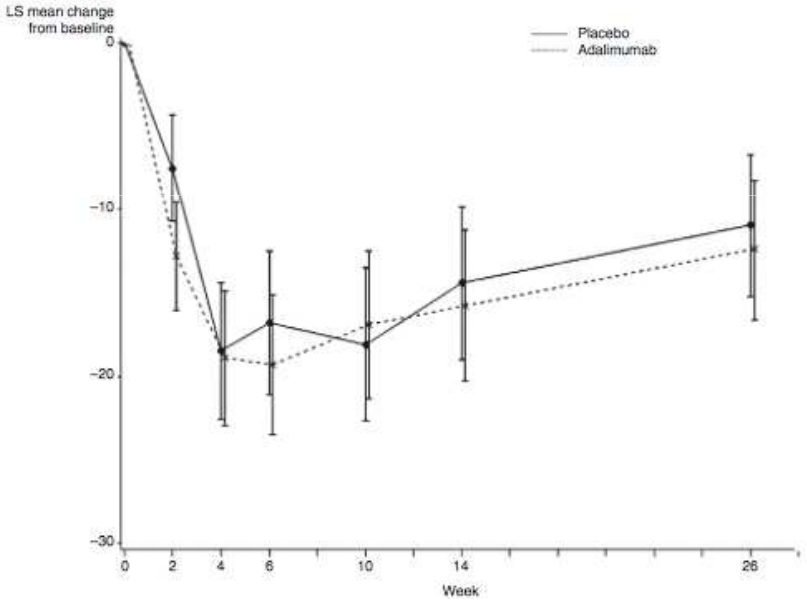
	Up to End of Study (0-40 wk), No. (%)		
	Tanezumab		
	2.5 mg (n = 231)	2.5/5 mg (n = 233)	Placebo (n = 232)
Overall Treatment-Emergent AEs			
Patients with AEs	156 (67.5)	143 (61.4)	145 (62.5)
Patients with treatment-related AEs	40 (17.3)	33 (14.2)	31 (13.4)
Patients discontinued treatment due to AEs	1 (0.4)	3 (1.3)	3 (1.3)
Patients with serious AEs	7 (3.0)	11 (4.7)	9 (3.9)
Treatment-Emergent Neurological AEs			
Abnormal peripheral sensation AEs occurring in ≥2% in any treatment group[b]			
Paresthesia	8 (3.5)	3 (1.3)	1 (0.4)
Hypoesthesia	5 (2.2)	6 (2.6)	6 (2.6)
Sympathetic nervous system AEs occurring in ≥1% in any treatment group[c]			
Diarrhea	5 (2.2)	8 (3.4)	4 (1.7)
Nausea	4 (1.7)	1 (0.4)	4 (1.7)
Orthostatic hypotension	3 (1.3)	1 (0.4)	1 (0.4)
Urinary incontinence	2 (0.9)	3 (1.3)	4 (1.7)
Sinus bradycardia	1 (0.4)	3 (1.3)	4 (1.7)
Joint Safety Outcomes			
Patients with adjudicated joint safety events			
Normal osteoarthritis progression	8 (3.5)	17 (7.3)	5 (2.2)
Rapidly progressive OA type 1[d]	3 (1.3)	1 (0.4)	0
Rapidly progressive OA type 2[e]	2 (0.9)	0	0
Other (eg, preexisting subchondral insufficiency fracture)[f]	1 (0.4)	0	0
Patients with ≥1 total joint replacement	8 (3.5)	16 (6.9)[g]	4 (1.7)
Joints replaced			
Knee	3	10	4
Hip	5	7	0

Katz JN. JAMA. 2019;322(1):30-1.

EXTENDED REPORT

Adalimumab in patients with hand osteoarthritis refractory to analgesics and NSAIDs: a randomised, multicentre, double-blind, placebo-controlled trial

X Chevalier,[1] P Ravaud,[2] E Maheu,[3] G Baron,[2] A Rialland,[4] P Vergnaud,[5] C Roux,[6] Y Maugars,[7] D Mulleman,[8] C Lukas,[9] D Wendling,[10] P Lafforgue,[11] D Loeuille,[12] V Foltz,[13] P Richette,[14] On behalf of the French section of osteoarthritis



Chevalier X. Ann Rheum Dis. 2015;74:1697-705.

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

A randomised double-blind placebo-controlled crossover trial of HUMira (adalimumab) for erosive hand OsteoaRthritis – the HUMOR trial

D. Aitken †, L.L. Laslett †, F. Pan †, I.K. Haugen ‡, P. Otahal †, N. Bellamy § ||, P. Bird ¶, G. Jones † *

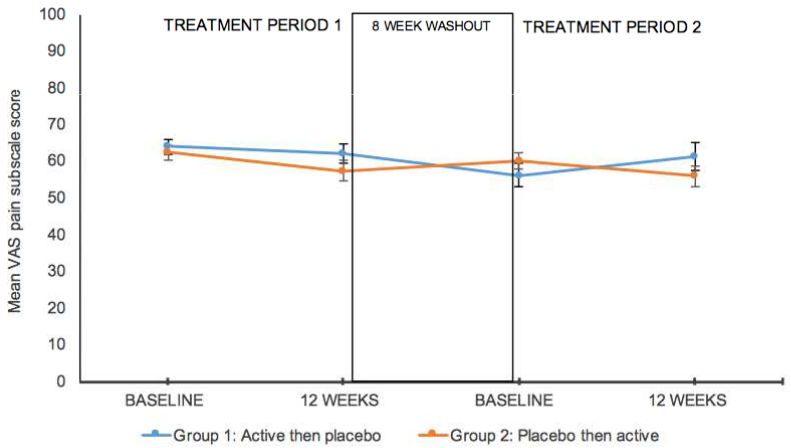
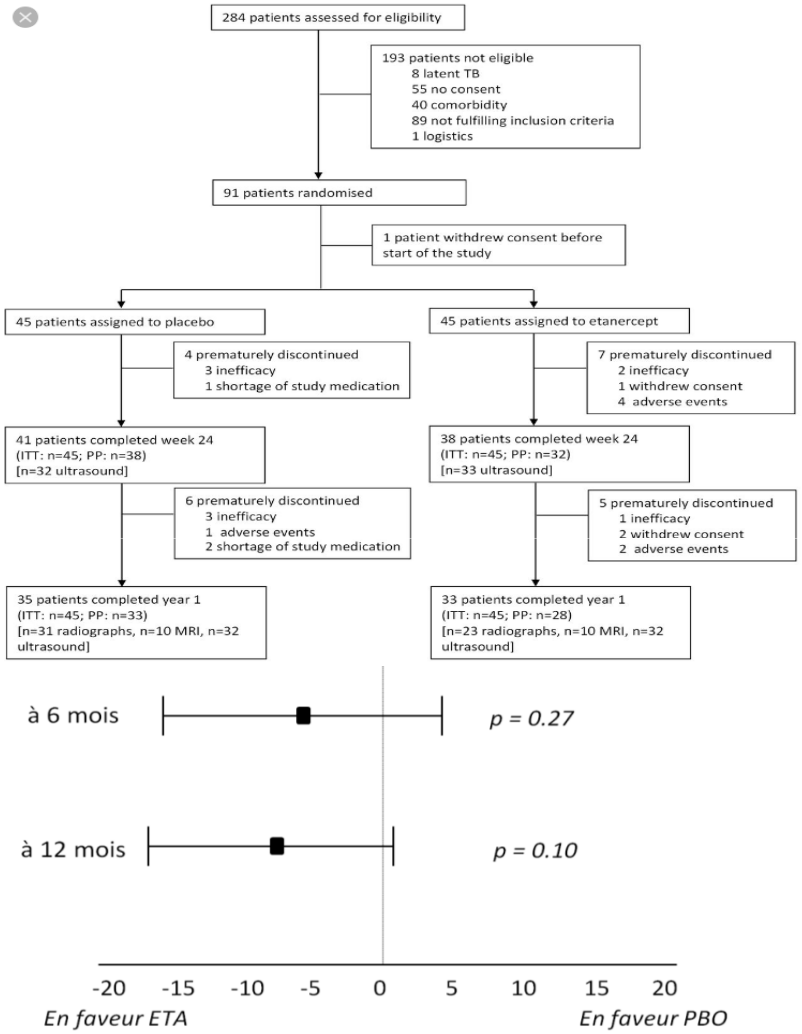
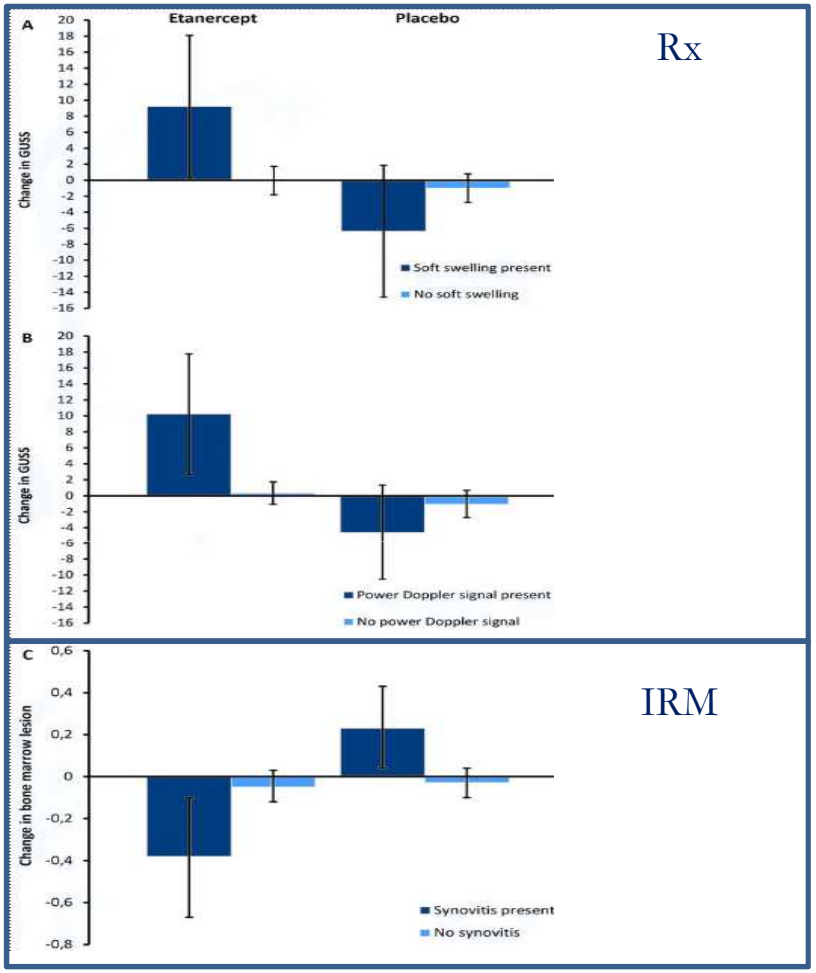


Fig. 2. Mean VAS pain score ± standard error over each 12-week treatment period.

Aitken D. Osteoarthritis Cartilage. 2018;26:880-7.





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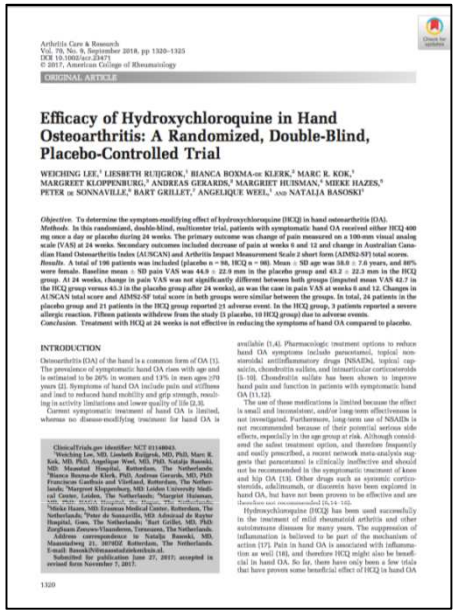
Kloppenburg M. Ann Rheum Dis. 2018;77:1757-64.



Arthritis Care & Research
Vol. 70, No. 9, September 2018, pp 1320–1325
DOI 10.1002/acr.23477
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ORIGINAL ARTICLE

Efficacy of Hydroxychloroquine in Hand Osteoarthritis: A Randomized, Double-Blind, Placebo-Controlled Trial

WEICHING LEE,[1] LIESBETH RUIJGROK,[2] BIANCA BOXMA-DE KLERK,[2] MARC R. KOK,[3] MARGREET KLOPPENBURG,[4] ANDREAS GERARDS,[4] MARGRIET HUISMAN,[5] MIEKE HAZES,[6] PETER DE SONNAVILLE,[6] BART GRILLET,[7] ANGELIQUE WEEL,[1] AND NATALJA BASOSKI[1]

Objective. To determine the symptom-modifying effect of hydroxychloroquine (HCQ) in hand osteoarthritis (OA).

Methods. In this randomized, double-blind, multicenter trial, patients with symptomatic hand OA received either HCQ 400 mg once a day or placebo during 24 weeks. The primary outcome was change of pain measured on a 100-mm visual analog scale (VAS) at 24 weeks. Secondary outcomes included decrease of pain at weeks 6 and 12 and change in Australian Canadian Hand Osteoarthritis Index (AUSCAN) and Arthritis Impact Measurement Scales 2 short form (AIMS2-SF) total scores.

Results. A total of 196 patients was included (placebo n = 98, HCQ n = 98). Mean ± SD age was 58.8 ± 7.6 years, and 86% were female. Baseline mean ± SD pain VAS was 44.9 ± 22.9 mm in the placebo group and 43.2 ± 22.3 mm in the HCQ group. At 24 weeks, change in pain VAS was not significantly different between both groups (imputed mean VAS 42.7 in the HCQ group versus 45.3 in the placebo group after 24 weeks), as was the case in pain VAS at weeks 6 and 12. Changes in AUSCAN total score and AIMS2-SF total score in both groups were similar between the groups. In total, 24 patients in the placebo group and 21 patients in the HCQ group reported 25 adverse event. In the HCQ group, 3 patients reported a severe allergic reaction. Fifteen patients withdrew from the study (5 placebo, 10 HCQ group) due to adverse events.

Conclusion. Treatment with HCQ at 24 weeks is not effective in reducing the symptoms of hand OA compared to placebo.

INTRODUCTION

Osteoarthritis (OA) of the hand is a common form of OA [1]. The prevalence of symptomatic hand OA rises with age and is estimated to be 26% in women and 13% in men ages ≥70 years [2]. Symptoms of hand OA include pain and stiffness and lead to reduced hand mobility and grip strength, resulting in activity limitations and lower quality of life [2,3].

Current symptomatic treatment of hand OA is limited, whereas no disease-modifying treatment for hand OA is available [1,4]. Pharmacologic treatment options to reduce hand OA symptoms include paracetamol, topical nonsteroidal antiinflammatory drugs (NSAIDs), topical capsaicin, chondroitin sulfate, and intraarticular corticosteroids [5–10]. Chondroitin sulfate has been shown to improve hand pain and function in patients with symptomatic hand OA [11,12].

The use of these medications is limited because the effect is small and inconsistent, and/or long-term effectiveness is not investigated. Furthermore, long-term use of NSAIDs is not recommended because of their potential serious side effects, especially in the age group at risk. Although considered the safest treatment option, and therefore frequently and easily prescribed, a recent network meta-analysis suggests that paracetamol is clinically ineffective and should not be recommended in the symptomatic treatment of knee and hip OA [13]. Other drugs such as systemic corticosteroids, colchicinoids, or diacerein have been explored in hand OA, but have not been proven to be effective and are therefore not recommended [6,14–16].

Hydroxychloroquine (HCQ) has been used successfully in the treatment of mild rheumatoid arthritis and other autoimmune diseases for many years. The suppression of inflammation is believed to be part of the mechanism of action [17]. Pain in hand OA is associated with inflammation as well [18], and therefore HCQ might also be beneficial in hand OA. So far, there have only been a few trials that have proven some beneficial effect of HCQ in hand OA

ClinicalTrials.gov identifier: NCT 01140841.

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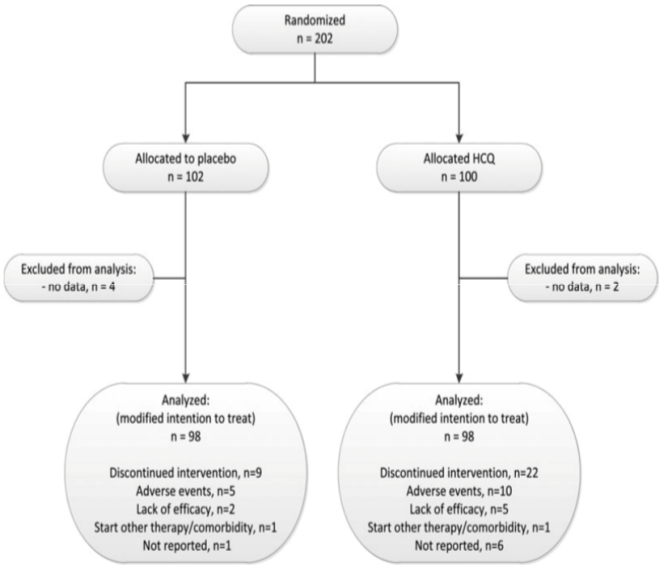
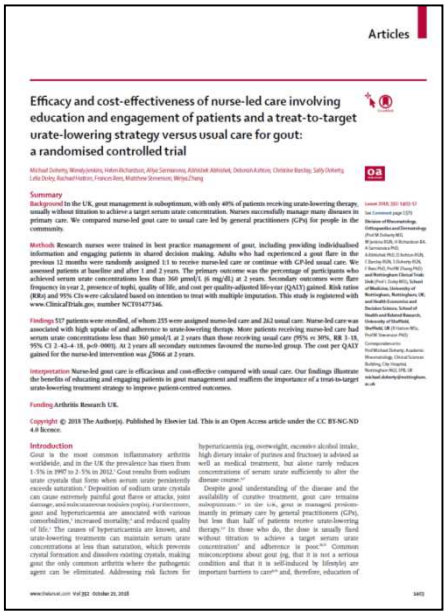


Table 2. Outcome measures of imputed data over 6, 12, and 24 weeks in 196 patients with hand osteoarthritis who received either hydroxychloroquine (HCQ) or placebo*

Outcome	Placebo	HCQ	*P*
Pain VAS			
Week 6	41.9 (37.6, 46.3)	43.7 (39.2, 48.2)	0.57†
Week 12	42.2 (37.6, 46.7)	43.8 (40.0, 49.6)	0.43‡
Week 24	45.3 (40.4, 50.3)	42.7 (37.6, 47.8)	0.45§
AUSCAN total score			
Week 6	48.5 (45.9, 51.2)	49.0 (46.3, 51.8)	0.81†
Week 12	49.3 (46.4, 52.2)	48.0 (44.8, 51.0)	0.52‡
Week 24	48.7 (45.2, 52.3)	46.8 (43.1, 50.5)	0.46§
AIMS2-SF total score			
Week 6	37.6 (35.8, 39.5)	37.8 (35.9, 39.6)	0.91†
Week 12	36.6 (34.7, 38.5)	37.3 (35.4, 39.3)	0.57‡
Week 24	36.9 (35.0, 38.8)	36.9 (34.9, 38.8)	0.99§

Lee W. Arthritis Care Res (Hoboken). 2018;70:1320-5.



Articles

Efficacy and cost-effectiveness of nurse-led care involving education and engagement of patients and a treat-to-target urate-lowering strategy versus usual care for gout: a randomised controlled trial

Michael Doherty, Wendy Jenkins, Helen Richardson, Afiya Sarmanova, Abhishek Abhishek, Deborah Ashton, Christine Barclay, Sally Doherty, Lelia Dickey, Rachael Hattton, Frances Rees, Matthew Stevenson, Weiya Zhang

Summary

Background In the UK, gout management is suboptimum, with only 40% of patients receiving urate-lowering therapy, usually without titration to achieve a target serum urate concentration. Nurses successfully manage many diseases in primary care. We compared nurse-led gout care to usual care led by general practitioners (GPs) for people in the community.

Methods Research nurses were trained in best practice management of gout, including providing individualised information and engaging patients in shared decision making. Adults who had experienced a gout flare in the previous 12 months were randomly assigned 1:1 to receive nurse-led care or continue with GP-led usual care. We assessed patients at baseline and after 1 and 2 years. The primary outcome was the percentage of participants who achieved serum urate concentrations less than 360 μmol/L (6 mg/dL) at 2 years. Secondary outcomes were flare frequency in year 2, presence of tophi, quality of life, and cost per quality-adjusted life-year (QALY) gained. Risk ratios (RRs) and 95% CIs were calculated based on intention to treat with multiple imputation. This study is registered with www.ClinicalTrials.gov, number NCT01477346.

Findings 517 patients were enrolled, of whom 255 were assigned nurse-led care and 262 usual care. Nurse-led care was associated with high uptake of and adherence to urate-lowering therapy. More patients receiving nurse-led care had serum urate concentrations less than 360 μmol/L at 2 years than those receiving usual care (95% vs 30%, RR 3·18, 95% CI 2·42–4·18, p<0·0001). At 2 years all secondary outcomes favoured the nurse-led group. The cost per QALY gained for the nurse-led intervention was £9066 at 2 years.

Interpretation Nurse-led gout care is efficacious and cost-effective compared with usual care. Our findings illustrate the benefits of educating and engaging patients in gout management and reaffirm the importance of a treat-to-target urate-lowering treatment strategy to improve patient-centred outcomes.

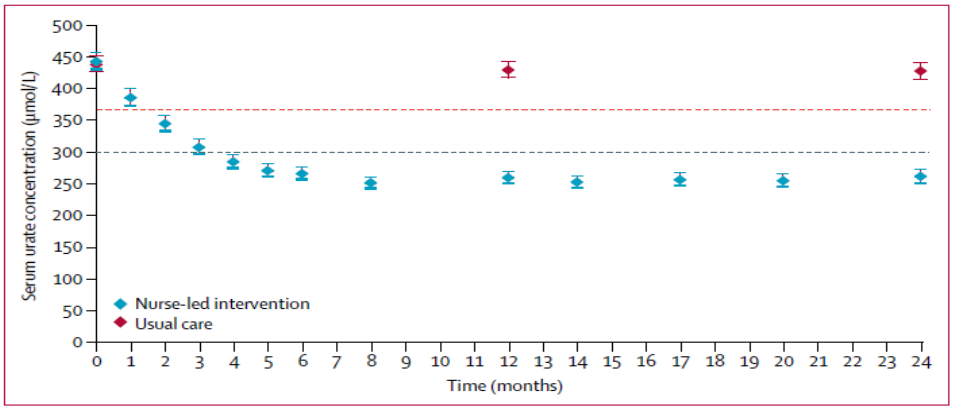
Funding Arthritis Research UK.

Introduction

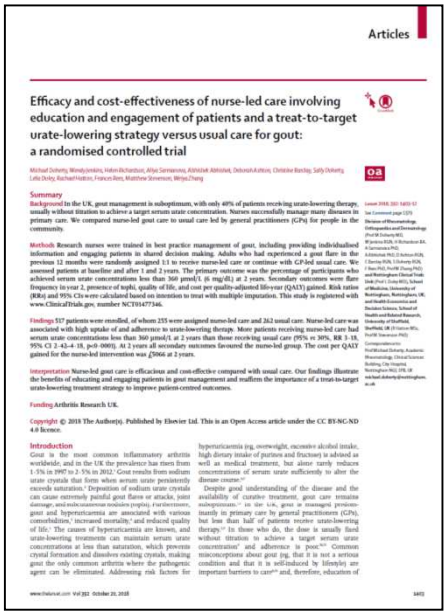
Gout is the most common inflammatory arthritis worldwide, and in the UK the prevalence has risen from 1·5% in 1997 to 2·5% in 2012.[1] Gout results from sodium urate crystals that form when serum urate persistently exceeds saturation.[2] Deposition of sodium urate crystals can cause extremely painful gout flares or attacks, joint damage, and musculoskeletal disability. Furthermore, gout and hyperuricaemia are associated with various comorbidities,[3] increased mortality,[4] and reduced quality of life.[5] The causes of hyperuricaemia are known, and urate-lowering treatments can maintain serum urate concentrations at less than saturation, which prevents crystal formation and dissolves existing crystals, making gout the only common arthritis where the pathogenic agent can be eliminated. Addressing risk factors for hyperuricaemia (eg, overweight, excessive alcohol intake, high dietary intake of purines and fructose) is advised as well as medical treatment, but alone rarely reduces concentrations of serum urate sufficiently to alter the disease course.[6,7]

Despite good understanding of the disease and the availability of curative treatment, gout care remains suboptimum,[1,8] in the UK, gout is managed predominantly in primary care by general practitioners (GPs), but less than half of patients receive urate-lowering therapy.[1,9] In those who do, the dose is usually fixed without titration to achieve a target serum urate concentration[9] and adherence is poor.[10,11] Common misconceptions about gout (eg, that it is not a serious condition and that it is self-induced by lifestyle) are important barriers to care[8,9] and, therefore, education of

	Nurse-led care (n=255)	Usual care (n=262)	Mean difference (95% CI)
Serum urate concentration (μmol/L)			
Baseline	443·07 (100·50)	438·85 (98·17)	4·22 (–12·97 to 21·40)
1 year	250·56 (60·59)	427·87 (103·65)	178·86 (164·80 to 192·92)
2 years	251·52 (72·15)	421·13 (109·62)	170·98 (154·37 to 187·58)
p for trend within group	<0·0001	0·0647	
Number of tophi			
Baseline	2 (1–4)	2 (1–3)	0·28 (–2·89 to 3·45)
1 year	1 (1–3)	1 (1–2)	2·19 (0·77 to 3·61)
2 years	1 (1–1)	1 (1–2)	2·06 (0·94 to 3·19)
p for trend within group	0·0010	0·3784	..
Diameter of largest tophus (mm)			
Baseline	16·89 (14·08)	20·09 (13·25)	–3·20 (–10·73 to 4·32)
1 year	7·53 (11·34)	16·54 (16·27)	7·18 (1·08 to 13·28)
2 years	3·29 (7·89)	13·61 (15·06)	8·77 (3·75 to 13·79)
p for trend within group	<0·0001	0·1478	..
SF-36 score			
Physical component			
Baseline	35·64 (14·20)	35·48 (14·29)	0·16 (–2·31 to 2·62)
1 year	40·46 (14·10)	36·54 (14·21)	3·82 (1·88 to 5·76)
2 years	41·01 (16·71)	37·43 (14·80)	3·48 (1·20 to 5·75)
p for trend within group	<0·0001	0·1371	..



Doherty M. Lancet. 2018;392:1403-12.



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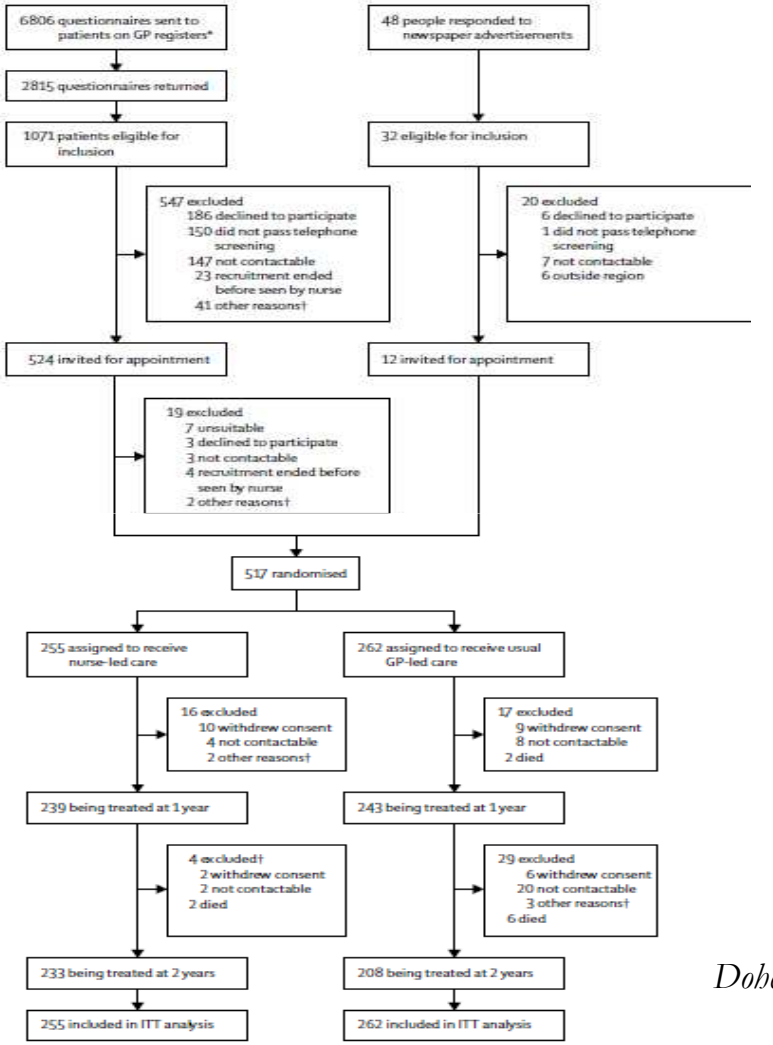

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AJKD Original Investigation

Febuxostat Therapy for Patients With Stage 3 CKD and Asymptomatic Hyperuricemia: A Randomized Trial

Kenjiro Kimura, Tatsuo Hosoya, Shunya Uchida, Masaaki Inaba, Hirofumi Makino, Shoichi Maruyama, Sadayoshi Ito, Tetsuya Yamamoto, Yasuhiko Tomino, Iwao Ohno, Yugo Shibagaki, Satoshi Iimuro, Naohiko Imai, Masanari Kuwabara, Hiroshi Hayakawa, Hiroshi Ohtsu, and Yasuo Ohashi; on behalf of the FEATHER Study Investigators

Rationale & Objective: Epidemiologic and clinical studies have suggested that urate-lowering therapy may slow the progression of chronic kidney disease (CKD). However, definitive evidence is lacking.

Study Design: Randomized, double-blind, placebo-controlled trial.

Setting & Participants: 467 patients with stage 3 CKD and asymptomatic hyperuricemia at 55 medical institutions in Japan.

Intervention: Participants were randomly assigned in a 1:1 ratio to receive febuxostat or placebo for 108 weeks.

Outcomes: The primary end point was the slope (in mL/min/1.73 m^2 per year) of estimated glomerular filtration rate (eGFR). Secondary end points included changes in eGFRs and serum uric acid levels at 24, 48, 72, and 108 weeks of follow-up and the event of doubling of serum creatinine level or initiation of dialysis therapy.

Results: Of 443 patients who were randomly assigned, 219 and 222 assigned to febuxostat and placebo, respectively, were included in the analysis. There was no significant difference in mean eGFR slope between the febuxostat (0.23 ± 5.26 mL/min/1.73 m^2 per year) and placebo (−0.47 ± 4.48 mL/min/1.73 m^2 per year) groups (difference, 0.70; 95% CI, −0.21 to 1.62; $P = 0.1$). Subgroup analysis demonstrated a significant benefit from febuxostat in patients without proteinuria ($P = 0.005$) and for whom serum creatinine concentration was lower than the median ($P = 0.009$). The incidence of gouty arthritis was significantly lower ($P = 0.007$) in the febuxostat group (0.91%) than in the placebo group (5.86%). Adverse events specific to febuxostat were not observed.

Limitations: GFR was estimated rather than measured, and patients with stages 4 and 5 CKD were excluded.

Conclusions: Compared to placebo, febuxostat did not mitigate the decline in kidney function among patients with stage 3 CKD and asymptomatic hyperuricemia.

Funding: Funded by Teijin Pharma Limited.

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Complete author and article information, including a list of the FEATHER Study Investigators, provided before references.

K.K. and T.H. contributed equally to this work.

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Previous clinical studies have indicated that hyperuricemia is a potentially modifiable risk factor for the development and progression of chronic kidney disease (CKD).[1-4] Some small controlled clinical studies have shown that urate-lowering therapy with allopurinol can retard CKD progression.[5-8] Nevertheless, sufficient clinical evidence to support widespread use of the therapy to slow CKD progression is not available.[1] Furthermore, information for the effects of xanthine oxidase inhibitors on early kidney damage is sparse or lacking.[9]

Editorial, p. 776

Febuxostat, a novel potent nonpurine-selective inhibitor of xanthine oxidase for oral use, is metabolized predominantly in the liver by glucuronidation, with only 1% to 6% of the dose being excreted unchanged through the kidneys.[10] Hence, decreased glomerular filtration rate (GFR) has little impact on the pharmacokinetic profile of febuxostat,[11] allowing its safe administration for patients with low GFRs.

In consideration of the demand for an adequately powered randomized trial to evaluate the benefits and risks of urate-lowering therapy in patients with CKD,[12] we conducted the present study to test the hypothesis that febuxostat is superior to placebo in suppressing estimated GFR (eGFR) decline in Japanese patients with stage 3 CKD who had asymptomatic hyperuricemia.

Methods

Patients

Patients were eligible for enrollment if they were 20 years or older, had hyperuricemia (uric acid concentration > 7.0-10.0 mg/dL), had stage 3 CKD,[13] had no history of gout, and provided written informed consent. eGFR was calculated according to the equation defined by the Japanese Society of Nephrology.[13] Key exclusion criteria were patients who had poorly controlled diabetes mellitus (DM; hemoglobin $A_{1c} \geq 8.4\%$ in the National Glycohemoglobin Standardization Program), systolic blood pressure (SBP) ≥ 160 mm Hg, diastolic blood pressure (DBP) ≥ 100 mm Hg, alanine or

Table 1. Characteristics of Study Participants at Baseline

	Placebo (n = 222)	Febuxostat (n = 219)	P
Demographic and Clinical Characteristics			
Age, y	65.4 ± 12.3	65.3 ± 11.8	0.9[a]
Age category			
<65 y	90 (40.5%)	90 (41.1%)	
65-74 y	75 (33.8%)	81 (37.0%)	
≥75 y	57 (25.7%)	48 (21.9%)	
Male sex	171 (77.0%)	170 (77.6%)	0.9[b]
Diabetes mellitus	68 (30.6%)	64 (29.2%)	0.8[b]
Proteinuria	103 (46.4%)	107 (48.9%)	0.6[b]
CKD stage			0.9[b]
3a	106 (47.7%)	106 (48.4%)	
3b	116 (52.3%)	113 (51.6%)	
Smoking status			0.9[a]
Current smoker	29 (13.1%)	28 (12.8%)	
Former smoker	102 (45.9%)	103 (47.0%)	
Lifetime nonsmoker	91 (41.0%)	88 (40.2%)	
Body weight, kg	66.1 ± 11.2	66.1 ± 13.1	0.9[c]
Body mass index, kg/m^2	24.7 ± 3.6	24.9 ± 4.4	0.7[c]
Blood pressure			
Systolic, mm Hg	129.6 ± 14.9	132.5 ± 15.0	0.04[c]
Diastolic, mm Hg	77.3 ± 11.3	77.9 ± 10.7	0.6[c]
Coexisting conditions			
Ischemic heart disease	14 (6.3%)	19 (8.7%)	0.4[b]
Cerebrovascular disease	17 (7.7%)	29 (13.2%)	0.06[b]
Aortic disease	3 (1.4%)	7 (3.2%)	0.2[b]
Peripheral artery disease	4 (1.8%)	3 (1.4%)	0.9[b]
Lifestyle-related disease	207 (93.2%)	211 (96.3%)	0.2[b]
Medications			
ACE inhibitor and/or ARB	163 (73.4%)	181 (82.6%)	0.02[b]
Statins	74 (33.3%)	93 (42.5%)	0.05[b]
β-Blockers	30 (13.5%)	40 (18.3%)	0.2[b]
Antidiabetic drugs	52 (23.4%)	46 (21.0%)	0.6[b]
Diuretics	36 (16.2%)	45 (20.5%)	0.3[b]
Laboratory Results			
Serum uric acid, mg/dL	7.8 ± 0.9	7.8 ± 0.9	0.9[c]
Estimated GFR, mL/min/1.73 m^2	44.9 ± 9.7	45.2 ± 9.5	0.7[c]
Serum creatinine, mg/dL	1.3 ± 0.3	1.2 ± 0.3	0.7[c]
Hemoglobin A_{1c}, %	6.1 ± 0.7	6.0 ± 0.6	0.07[c]
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Table 3. Adverse Events Until Week 108 of Treatment

	Placebo (n = 222)	Febuxostat (n = 219)
No. of adverse events	135 (60.8)	124 (56.6)
Hypersensitivity (eg, rash and eruption)	10 [0]	7 [0]
Liver dysfunction[a]	9 [0]	4 [0]
Reduced eGFR[a]	13 [3]	8 [3]
Cardiovascular disorders (eg, MI, angina pectoris, HF, and aortic aneurysm)	7 [3]	4 [3]
Stroke (cerebral infarction, cerebral hemorrhage, and subarachnoid hemorrhage)	2 [2]	1 [1]
Other abnormalities	128 [33]	119 [44]
Respiratory (including infections)	42 [5]	33 [4]
Gastrointestinal	32 [9]	39 [12]
Infections	10 [0]	7 [0]
Musculoskeletal	37 [5]	34 [8]
Blood chemistry	11 [0]	8 [0]
Cardiovascular system	9 [3]	3 [2]
Blood pressure changes	8 [0]	3 [0]
Arrhythmias	3 [1]	4 [3]
Ophthalmologic	11 [4]	10 [6]
Otorhinolaryngologic	15 [3]	19 [1]
Oral surgical and dental	6 [0]	5 [1]
Urologic	11 [2]	6 [4]
Endocrinologic (including DM and dyslipidemia)	14 [1]	10 [4]
Dermatologic	9 [1]	10 [1]
Central nervous system	4 [2]	2 [1]
Death	1[a] [1]	1[c] [1]
Others	10 [2]	13 [1]

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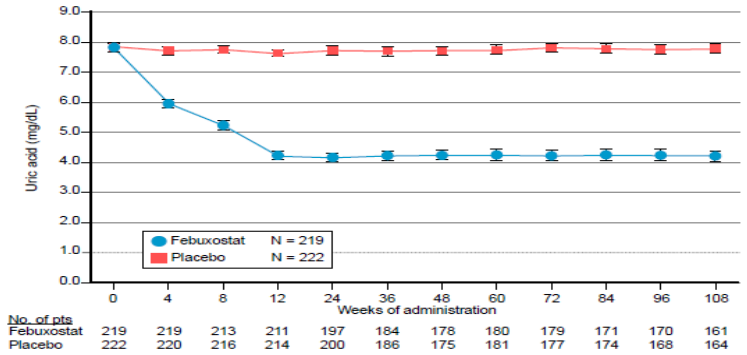
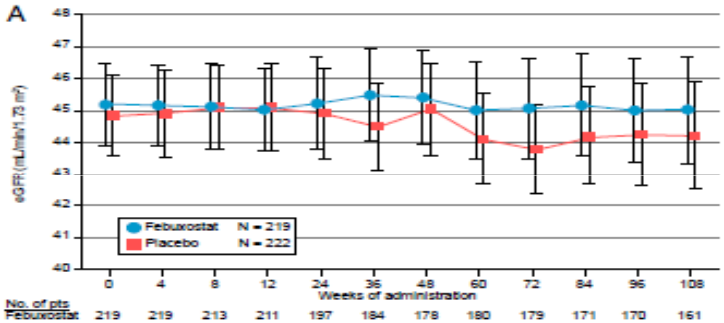


No. of pts												
Febuxostat	219	219	213	211	197	184	178	180	179	171	170	161
Placebo	222	220	216	214	200	186	175	181	177	174	168	164



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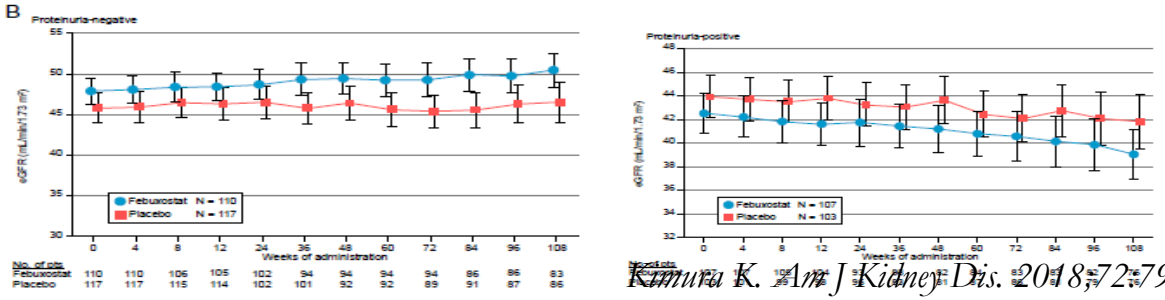
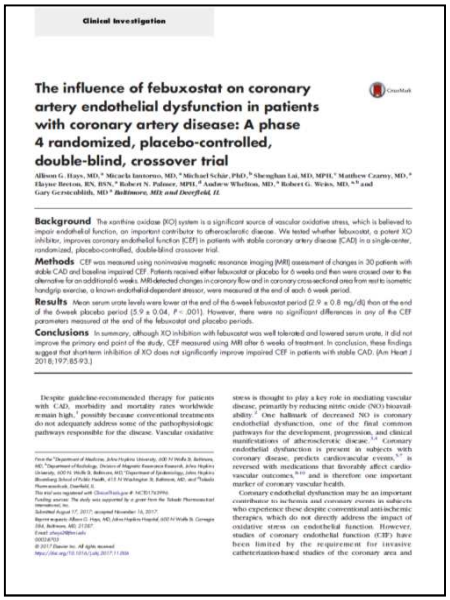


No. of pts												
Febuxostat	110	110	106	105	102	94	94	94	94	86	86	83
Placebo	117	117	115	114	102	101	92	92	89	91	87	86

Kimura K. Am J Kidney Dis. 2018;72:798-810.



Clinical Investigation

The influence of febuxostat on coronary artery endothelial dysfunction in patients with coronary artery disease: A phase 4 randomized, placebo-controlled, double-blind, crossover trial

Allison G. Hays, MD,[a] Micaela Iantorno, MD,[a] Michael Schär, PhD,[b] Shenghan Lai, MD, MPH,[c] Matthew Czarny, MD,[a] Eleyne Breton, RN, BSN,[a] Robert N. Palmer, MPH,[d] Andrew Whelton, MD,[d] Robert G. Weiss, MD,[a,b] and Gary Gerstenblith, MD[a] *Baltimore, MD; and Deerfield, IL*

Background The xanthine oxidase (XO) system is a significant source of vascular oxidative stress, which is believed to impair endothelial function, an important contributor to atherosclerotic disease. We tested whether febuxostat, a potent XO inhibitor, improves coronary endothelial function (CEF) in patients with stable coronary artery disease (CAD) in a single-center, randomized, placebo-controlled, double-blind crossover trial.

Methods CEF was measured using noninvasive magnetic resonance imaging (MRI) assessment of changes in 30 patients with stable CAD and baseline impaired CEF. Patients received either febuxostat or placebo for 6 weeks and then were crossed over to the alternative for an additional 6 weeks. MRI-detected changes in coronary flow and in coronary cross-sectional area from rest to isometric handgrip exercise, a known endothelial-dependent stressor, were measured at the end of each 6 week period.

Results Mean serum urate levels were lower at the end of the 6-week febuxostat period (2.9 ± 0.8 mg/dl) than at the end of the 6-week placebo period (5.9 ± 0.04, $P < .001$). However, there were no significant differences in any of the CEF parameters measured at the end of the febuxostat and placebo periods.

Conclusions In summary, although XO inhibition with febuxostat was well tolerated and lowered serum urate, it did not improve the primary end point of the study, CEF measured using MRI after 6 weeks of treatment. In conclusion, these findings suggest that short-term inhibition of XO does not significantly improve impaired CEF in patients with stable CAD. (Am Heart J 2018;197:85-93.)

Despite guideline-recommended therapy for patients with CAD, morbidity and mortality rates worldwide remain high,[1] possibly because conventional treatments do not adequately address some of the pathophysiologic pathways responsible for the disease. Vascular oxidative stress is thought to play a key role in mediating vascular disease, primarily by reducing nitric oxide (NO) bioavailability.[2] One hallmark of decreased NO is coronary endothelial dysfunction, one of the final common pathways for the development, progression, and clinical manifestations of atherosclerotic disease.[3,4] Coronary endothelial dysfunction is present in subjects with coronary disease, predicts cardiovascular events,[5,6] is reversed with medications that favorably affect cardiovascular outcomes,[7,8] and is therefore one important marker of coronary vascular health.

Coronary endothelial dysfunction may be an important contributor to ischemia and coronary events in subjects who experience these despite conventional anti-ischemic therapies, which do not directly address the impact of oxidative stress on endothelial function. However, studies of coronary endothelial function (CEF) have been limited by the requirement for invasive catheterization-based studies of the coronary area and

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This trial was registered with ClinicalTrials.gov # NCT01761994.
Funding source: The study was supported by a grant from the Takeda Pharmaceutical International, Inc.
Submitted August 17, 2017; accepted November 16, 2017.
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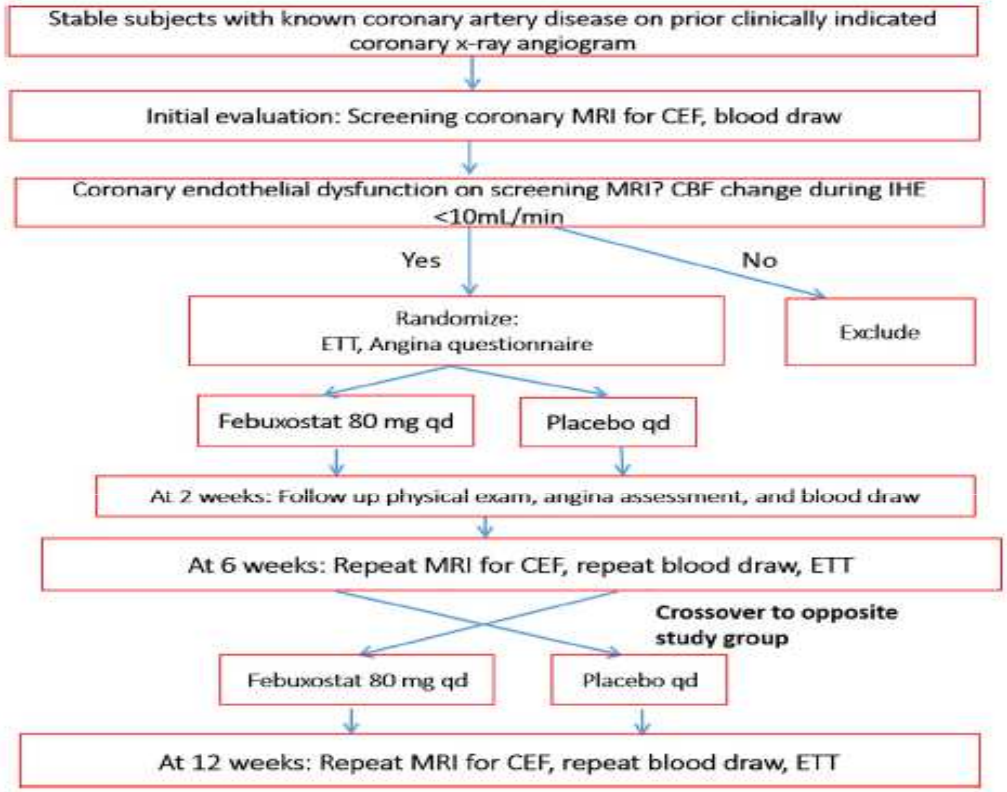
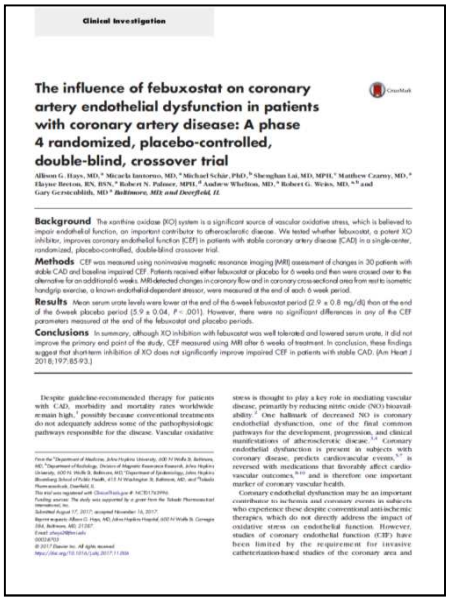
https://doi.org/10.1016/j.ahj.2017.11.006



Hays AG. Am Heart J. 2018;197:85-93.



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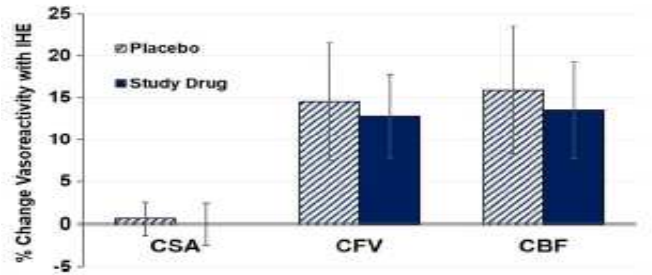
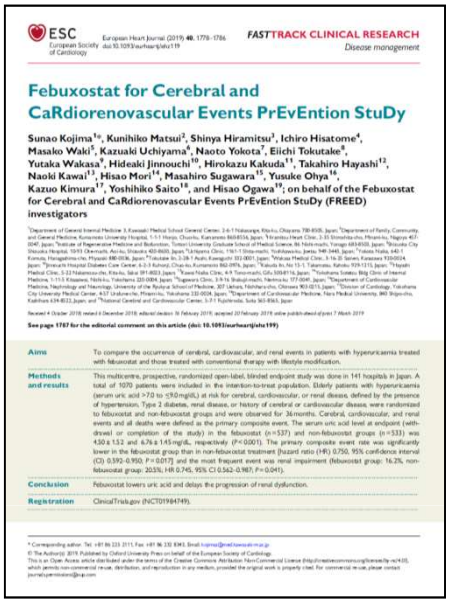


Parameter	n	Placebo Median	Placebo IQR	Placebo Mean	Placebo SE	Febuxostat Median	Febuxostat IQR	Febuxostat Mean	Febuxostat SE	*P* value
Exercise time (s)	30	716	650-790	702	30.4	710	640-851	713	31.1	.8
Exercise METs	30	7	6.8-9.4	7.6	0.4	7	6.6-9.7	7.6	0.4	.9
Time to ischemic ECG changes (s)	4	594	358-671	514	46	316	230-402	316	22	.15
Maximum ST segment change (mm)	4	1.0	1.0-1.5	1.3	0.09	1.5	1.0-2.0	1.5	0.13	.34

METs, Metabolic equivalents.

Parameter	Placebo n	Placebo %	Febuxostat n	Febuxostat %
Angina present	6	21%	9	31%
Angina class				
CCS class 1	5	17%	6	21%
CCS class 2	1	3.4%	3	10%
CCS class 3	0	0%	0	0%
CCS class 4	0	0%	0	0%

Hays AG. Am Heart J. 2018;197:85-93.



ESC European Society of Cardiology

European Heart Journal (2019) 40, 1778–1786 doi:10.1093/eurheartj/ehz119

FASTTRACK CLINICAL RESEARCH
Disease management

Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDy

Sunao Kojima[1]*, Kunihiko Matsui[2], Shinya Hiramitsu[3], Ichiro Hisatome[4], Masako Waki[5], Kazuaki Uchiyama[6], Naoto Yokota[7], Eiichi Tokutake[8], Yutaka Wakasa[9], Hideaki Jinnouchi[10], Hirokazu Kakuda[11], Takahiro Hayashi[12], Naoki Kawai[13], Hisao Mori[14], Masahiro Sugawara[15], Yusuke Ohya[16], Kazuo Kimura[17], Yoshihiko Saito[18], and Hisao Ogawa[19]; on behalf of the Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDy (FREED) investigators

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See page 1787 for the editorial comment on this article (doi: 10.1093/eurheartj/ehz199)

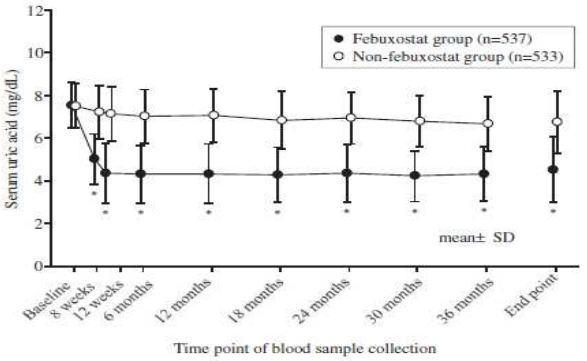
Aims To compare the occurrence of cerebral, cardiovascular, and renal events in patients with hyperuricaemia treated with febuxostat and those treated with conventional therapy with lifestyle modification.

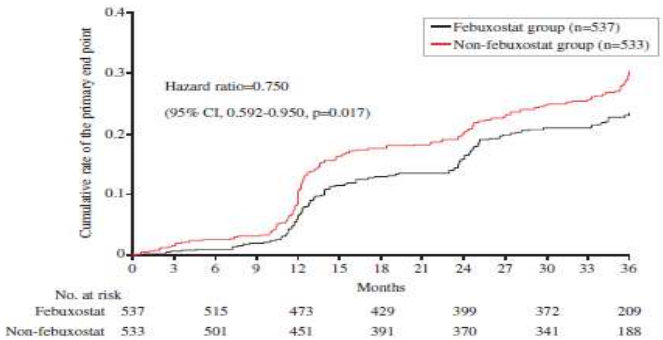
Methods and results This multicentre, prospective, randomized open-label, blinded endpoint study was done in 141 hospitals in Japan. A total of 1070 patients were included in the intention-to-treat population. Elderly patients with hyperuricaemia (serum uric acid >7.0 to <9.0 mg/dL) at risk for cerebral, cardiovascular, or renal disease, defined by the presence of hypertension, Type 2 diabetes, renal disease, or history of cerebral or cardiovascular disease, were randomized to febuxostat and non-febuxostat groups and were observed for 36 months. Cerebral, cardiovascular, and renal events and all deaths were defined as the primary composite event. The serum uric acid level at endpoint (withdrawal or completion of the study) in the febuxostat ($n = 537$) and non-febuxostat groups ($n = 533$) was 4.50 ± 1.52 and 6.76 ± 1.45 mg/dL, respectively ($P < 0.001$). The primary composite event rate was significantly lower in the febuxostat group than in non-febuxostat treatment [hazard ratio (HR) 0.750, 95% confidence interval (CI) 0.592–0.950, $P = 0.017$] and the most frequent event was renal impairment (febuxostat group: 16.2%, non-febuxostat group: 20.5%; HR 0.745, 95% CI 0.562–0.987, $P = 0.041$).

Conclusion Febuxostat lowers uric acid and delays the progression of renal dysfunction.

Registration ClinicalTrials.gov (NCT01984749).

* Corresponding author. Tel: +81 86 225 2111; Fax: +81 86 232 8343; Email: kojima@med.kawasaki-m.ac.jp





	Febuxostat group ($n = 537$)	Non-febuxostat group ($n = 533$)	Hazard ratio (95% confidence interval)	*P*-value
Primary endpoint				
Composite of death due to any cause, cerebrovascular disease, non-fatal coronary artery disease, heart failure requiring hospitalization, arteriosclerotic disease requiring treatment, renal impairment, and atrial fibrillation	125 (23.3)	153 (28.7)	0.750 (0.592–0.950)	0.017
Secondary endpoints				
Death due to cerebral, cardiovascular, or renal disease	6 (1.1)	6 (1.1)	0.958 (0.314–2.926)	0.940
Cerebrovascular disease	9 (1.7)	7 (1.3)	1.271 (0.479–3.371)	0.630
Non-fatal coronary artery disease	4 (0.7)	7 (1.3)	0.559 (0.167–1.869)	0.345
Heart failure requiring hospitalization	9 (1.7)	12 (2.3)	0.699 (0.290–1.689)	0.427
Arteriosclerotic disease requiring treatment	2 (0.4)	3 (0.6)	0.644 (0.107–3.873)	0.631
Renal impairment	87 (16.2)	109 (20.5)	0.745 (0.562–0.987)	0.041
Atrial fibrillation	4 (0.7)	3 (0.6)	1.320 (0.292–5.968)	0.719
Death due to other causes	4 (0.7)	6 (1.1)	0.635 (0.179–2.253)	0.482
Hard endpoint: composite of death due to any cause, cerebrovascular disease, or non-fatal coronary artery disease	23 (4.3)	26 (4.9)	0.861 (0.492–1.506)	0.600

Values are presented as *n* (%).
CI, confidence interval.

Kojima S. Eur Heart J. 2019;40:1778-86.

CLINICAL STUDY

Randomized Trial of Effect of Urate-Lowering Agent Febuxostat in Chronic Heart Failure Patients with Hyperuricemia (LEAF-CHF)

Study Design

Takashi Yokota,[1] MD, Arata Fukushima,[1] MD, Shintaro Kinugawa,[1] MD, Takahiro Okumura,[1] MD, Toyoaki Murohara,[2] MD and Hiroyuki Tsutsui,[3] MD

Summary

Hyperuricemia is an independent predictor of mortality in patients with chronic heart failure. The aim of the study is to determine whether a urate-lowering agent febuxostat, an inhibitor of xanthine oxidase, may improve the clinical outcomes in chronic heart failure patients with hyperuricemia when compared to conventional treatment. This multicenter, prospective, randomized, open-label, blinded endpoint study with a follow-up period of 24 weeks will enroll 200 Japanese chronic heart failure patients with hyperuricemia. The eligibility criteria include a diagnosis of chronic heart failure (New York Heart Association functional class II-III with a history of hospitalization due to worsening of heart failure within the last 2 years), reduced left ventricular systolic function (left ventricular ejection fraction < 40%) and increased plasma natriuretic peptide [plasma B-type natriuretic peptide (BNP) ≥ 100 pg/mL or N-terminal pro BNP (NT-proBNP) ≥ 400 pg/mL], and hyperuricemia (serum uric acid >7.0 mg/dL and ≤ 10 mg/dL) at the screening visit. The primary outcome is the difference in the plasma BNP levels between the baseline and 24 weeks of treatment. The plasma BNP levels are measured in the central laboratory in a blinded manner. This study investigates the efficacy and safety of febuxostat in chronic heart failure patients with hyperuricemia.

(Int Heart J 2018; 59: 976-982)

Key words: BNP, Oxidative stress, Xanthine oxidase inhibitor

Hyperuricemia is a common finding in patients with chronic heart failure (CHF) and is a known independent predictor of mortality and rehospitalization due to worsening heart failure (HF).[1-4] The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) reported that 56% of CHF patients had hyperuricemia with a higher incidence of all-cause and cardiac death, and rehospitalization due to worsening HF.[5] In addition, hyperuricemia is closely linked to the occurrence of atrial fibrillation, which can be a trigger of worsening HF.[6] The mechanism by which hyperuricemia is associated with worse clinical outcomes in CHF patients may be explained by the detrimental effects of uric acid (UA) on the vascular endothelium through the activation of inflammatory cytokines.[4] In patients with CHF, xanthine oxidase (XO) is highly activated, and increased reactive oxygen species (ROS) emission from XO in the vascular endothelium can cause endothelial dysfunction in the peripheral vessels, leading to increased cardiac afterload.[7] UA is produced via XO and, thus, it can be a useful marker for systemic oxidative stress in patients with CHF. Emerging evidence has drawn more attention to the effects of XO inhibitors on clinical outcomes.

Previous studies have shown that allopurinol, a widely used XO inhibitor for patients with hyperuricemia, may be effective in the treatment of cardiovascular disease.[8] High-dose allopurinol has been reported to reduce HF-related death in CHF patients.[9,10] In addition, previous studies have shown that in patients with CHF, allopurinol decreases B-type natriuretic peptide (BNP) levels,[11] which is known as a strong predictive biomarker of HF-related death.[12] However, a randomized trial to investigate the effect of oxypurinol, a metabolite of allopurinol, in patients with CHF did not improve clinical outcomes,[13] and a recent clinical trial using allopurinol also failed to improve clinical status, exercise capacity, quality of life, or cardiac function in hyperuricemic HF patients.[14]

Febuxostat, a novel urate-lowering agent for treatment against gout and hyperuricemia, inhibits XO via a different pathway from allopurinol. Febuxostat has demonstrated superiority to allopurinol in XO inhibition in vitro studies[15,16] and lowering serum UA in clinical studies.[17] Since febuxostat is finally eliminated via not only renal but also via hepatic pathways, it can be safely and

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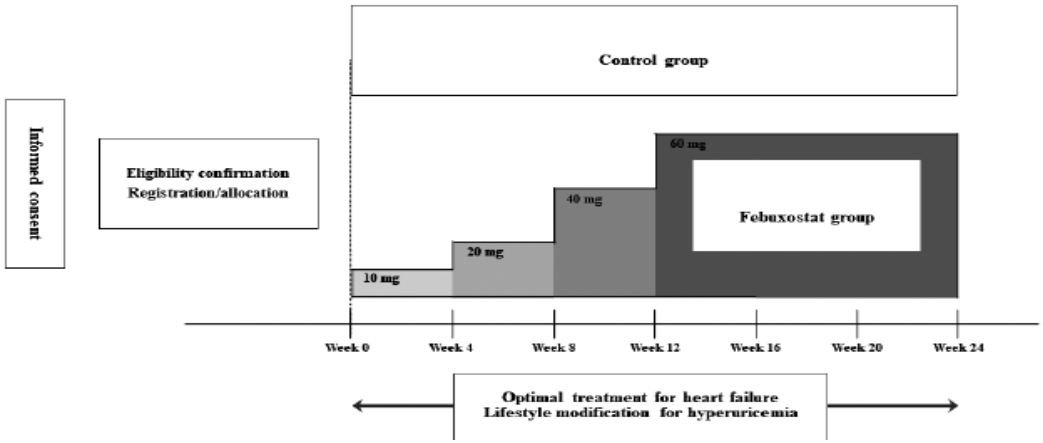
Table. Inclusion and Exclusion Criteria in the LEAF-CHF Study

		Criteria
Inclusion criteria	1	Male and female ambulatory patients aged ≥20 years at the time of enrollment with heart failure, or inpatients with stable heart failure when informed consent is obtained.
	2	Patients with hyperuricemia, as indicated by a serum uric acid level between > 7.0 mg/dL and ≤ 10.0 mg/dL at the time of enrollment.
	3	Chronic heart failure patients with stable NYHA functional class II to III with no change in the dose of the baseline therapies, including ACE-Is, ARBs, and β-blockers, within 4 weeks prior to enrollment.
	4	Patients with plasma BNP concentration ≥ 100 pg/mL or NT-proBNP concentration ≥ 400 pg/mL at the time of enrollment.
	5	LVEF < 40%, as measured by echocardiography within 8 weeks before enrollment.
	6	Eligible patients with a history of admission due to worsening heart failure before enrollment.
	7	Patients who provide written informed consent prior to participation.
Exclusion criteria	1	Patients who receive treatment with anti-hyperuricemic agents, including allopurinol, benzbromarone, probenecid, bucolome, topiroxostat, and febuxostat within 2 weeks prior to enrollment.
	2	Patients receiving mercaptopurine hydrate, azathioprine, vidarabine, and didanosine at the time of enrollment.
	3	Patients with a history of acute coronary syndrome or coronary revascularization within the last 3 months.
	4	Patients with valvular disease or congenital heart disease as the cause of heart failure.
	5	Patients with active gouty tophus or those who have symptoms of acute gouty arthritis within 1 year prior to enrollment.
	6	Patients who have serious liver disease, renal impairment (eGFR < 30 mL/minute or on dialysis), or malignancy.
	7	Patients with a history of hypersensitivity to febuxostat.
	8	Patients who are not appropriate for participation in this study as determined by the investigators.

ACE-I indicates angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; and NYHA, New York Heart Association.



Yokota T. Int Heart J. 2018;59:976-82.