Drug Evaluation
Future Rheumatology

Febuxostat, a novel drug for the treatment of hyperuricemia of gout

Fernando Perez-Ruiz†, Nicola Dalbeth & Naomi Schlesinger
†Author for correspondence: Rheumatology Division, Hospital de Cruces, Pza Cruces sn, 48903 Baracaldo, Vizcaya, Spain ■ Tel.: +34 946 006 470 ■ Fax: +34 944 905 985 ■ fernando.perezruiz@osakidetza.net

Febuxostat is a novel, nonpurine, selective inhibitor of xanthine oxidase (NP-SIXO), recently approved in the European Union. Febuxostat shows high, long-term efficacy for the reduction of serum urate (SU) levels, showing linear pharmacokinetics at approved doses, and its pharmacokinetics are not clinically significantly influenced by the presence of mild-to-moderate renal or liver function impairment. The clinical applicability of febuxostat should have a significant impact in patients with the highest baseline SU levels, the most severe gout, previous adverse events with other urate-lowering drugs or no availability of alternative urate-lowering drugs after failure to properly control SU levels during urate-lowering therapy. Febuxostat may become an interesting choice in our use of xanthine oxidase inhibitors.

Gout is the most common inflammatory arthritis affecting men, and is an increasing problem worldwide. The symptoms and signs of gout occur owing to deposition of monosodium urate (MSU) crystals that induce both acute and chronic inflammation. MSU crystals nucleate as a consequence of long-term hyperuricemia, for example, serum urate (SU) levels over the threshold for saturation of urate in plasma, close to 6.8 mg/dl.

The burden of gout has to be considered as the prevalence of gout is increasing, probably due to the longer life expectations of the population in developed countries [1]. Although commonly considered to be a mild disease, studies on the natural evolution of the untreated gout show that subcutaneous tophi or x-ray alterations were present in 40% of patients at 5-year follow-up [2], and follow-up studies also show that patients with insufficient reduction of SU levels show progression of tophi and x-ray changes [3].

The aim of the therapy of gout is to achieve dissolution of MSU crystals through a long-term reduction of SU levels below the threshold for saturation of urate [4]. In order to achieve MSU crystal dissolution, long-term urate-lowering therapy that achieves a SU of less than 6 mg/dl (360 µmol/l) is recommended [5]. This level is associated with improvement of several outcomes, such as acute episodes of inflammation and macroscopic deposition disappearance [6].

Although the milestone for the therapy of gout is to reduce SU levels in the long-term below the threshold for saturation of urate, only one in four patients on urate-lowering therapy achieve SU levels under 6 mg/dl [7]. Patients are very infrequently prescribed doses of allopurinol over 300 mg/day, and poor long-term compliance has been reported [8].

Until very recently, no new drugs had been registered for the past 40 years for the treatment of hyperuricemia of gout, with probenecid, sulfinpyrazone, benzbromarone and allopurinol being used to treat this condition [9–11]. In addition to febuxostat, other new drugs are in development for the treatment of hyperuricemia, such as a pegloticase (a polyethylenglicol-uricase) [12], Y-700 (an inhibitor of xanthine oxidoreductase) [13] and RDEA806 (a prodrug for RDEA594, a metabolite with uricosuric properties through inhibition of URAT1 activity) [14,15].

As with any drug that has been used for such a long time, the urate-lowering drugs (ULDs) available today show known limitations in tolerability, efficacy and clinical applicability in patients with co-morbidities (especially in patients with renal function impairment that may handicap the efficacy of some uricosuric drugs or increase the risk of side effects to allopurinol). Recent efforts and advances in development of new ULDs have culminated in the recent registration in the European Union of febuxostat for the treatment of hyperuricemia of gout.

Chemistry, pharmacodynamics & pharmacokinetics

Febuxostat (2-[3-cyano-4-(2-methylpropoxy) phenyl]-4-methylthiazole-5-carboxylic acid) (TEI-6720, TMX-67) is a nonpurine, selective inhibitor of xanthine oxidase/xanthine dehydrogenase (NP-SIXO). *In vitro* studies have shown

Keywords
febuxostat ■ gout ■ urate-lowering agents

future medicine part of fsg

that febuxostat displays potent mixed-type inhibition of both the oxidized and reduced forms of xanthine oxidase (XO) [16]. In addition, even at high concentrations, there is no effect on the other enzymes involved in purine and pyrimidine metabolism, such as guanine deaminase, hypoxanthine-guanine phosphoribosyltransferase, purine nucleoside phosphorylase, orotate phosphoribosyltransferase and orotidine-5′-monophosphate decarboxylase [16].

The mechanism of action is achieved through binding in a long, narrow channel leading to the molybdenum-pterin active site of XO, filling most of the channel and the immediate environment of the cofactor. It inhibits the activity of XO enzyme through the inhibition of substrate binding [17]. In rodent models, febuxostat was shown to display a more potent inhibition of XO than allopurinol [18]. In addition, the urate-lowering effect of febuxostat was more potent than that of allopurinol when tested in chimpanzees [19].

Oral febuxostat is well absorbed, with over 80% bioavailability. Concomitant administration of food or antiacids does not influence its urate-lowering effect, although a decrease in the AUC (range 16–19%) was observed when doses ranging from 40 to 120 mg were administered 30 min after food [20]. In Phase I dose-escalation studies, t_{max} ranged from 0.5 to 1.25 h, and the pharmacokinetics remained linear in the range of 10–120 mg doses, although an increase of the AUC of febuxostat was observed at doses higher than 120 mg [21].

Febuxostat is metabolized mainly through glucuronidation and oxidation in the liver [22,23], and less than 5% of the dose is excreted unchanged in the urine [23,24]. Studies on the interaction of febuxostat with indomethacin and naproxen – NSAIDs commonly prescribed to treat the episodes of acute inflammation in gout – showed no interaction considered to be clinically relevant, although naproxen caused an increase in plasma exposure to febuxostat [25]. Febuxostat did not influence the plasma protein binding of ibuprofen or warfarin, showing that it is unlikely that febuxostat causes a drug–drug interaction by binding to albumin [26]. In addition, no clinically significant interaction was observed between hydrochlorothiazide and febuxostat [27]. In addition, examination of the inhibitory effect of febuxostat on cytochrome P450 (CYP) enzymes suggests that febuxostat only minimally inhibits the activities of any CYP [26].

As febuxostat metabolism is mainly hepatic, and little intact drug is excreted through the kidneys, the pharmacokinetics of febuxostat do not seem to be greatly influenced by the presence of mild-to-moderate renal function impairment [28]. In a limited number of patients, the presence of even moderate-to-severe renal function impairment did not affect the urate-lowering properties of febuxostat [29]. However, the pharmacokinetics and safety of this drug in patients with end-stage renal disease is not known. An additional study showed that the pharmacokinetics and pharmacodynamics of febuxostat – at 80 mg doses – are not influenced significantly by the presence of mild-to-moderate liver function impairment [30]. In a Phase II study, the pharmacokinetics and pharmacodynamics of febuxostat did not differ in patients with hyperuricemia and/or gout from that observed in healthy subjects [24].

Since the metabolism of thiopurines is dependant on XO/xanthine dehydrogenase, great caution should be taken in co-prescribing febuxostat to patients on azathioprine. In this situation, febuxostat (and allopurinol) may lead to severe myelosuppression owing to blockade of azathioprine metabolism through XO inhibition [31].

In summary, febuxostat pharmacokinetics do not seem to be influenced by mild-to-moderate renal dysfunction or mild-to-moderate liver disease, and febuxostat does not influence CYP activity and shows no clinically significant interaction with ibuprofen, warfarin or thiazides.

Clinical efficacy

The clinical efficacy of febuxostat has been tested in several prospective, parallel, randomized, controlled studies. Phase I–II studies were placebo-controlled [32,33], while in Phase III studies febuxostat was compared with allopurinol [34,35]. Also, results from extension studies from the Phase II (Febuxostat Open-label Clinical trial of Urate-lowering efficacy and Safety [FOCUS]) and Phase III (fEbuXostat Comparative Extension Long-term [EXCEL]) clinical trials are available in abstract form [36,37].

In a Phase I, 2-week, multiple-dose, dose-escalation, placebo-controlled clinical trial, febuxostat was tested in 154 healthy subjects of both genders [33]. Doses from 10 to 120 mg showed a linear dose-dependent reduction of SU levels, proportional to C_{max} and AUC values. The reduction of SU ranged from 25 to 70% of baseline SU [33].

A Phase II, placebo-controlled 28-day duration comparative study was used to test different (40, 80 and 120 mg *per os* daily) febuxostat doses for clinical applicability in a 1:1:1:1 randomization schedule [32]. Patients with clinically significant chronic renal insufficiency (defined as serum creatinine over 1.5 mg/dl or estimated creatinine clearance

lower than 50 ml/min) were not included. Tophi were present in 16–29% of patients, and mean SU at baseline exceeded 9 mg/dl in all randomization groups, suggesting that the population studied was a severe one. In the intent-to-treat analysis at day 28, from 140 patients with baseline SU levels of at least 8 mg/dl, 94% of patients on febuxostat 120 mg/day, 76% of patients on febuxostat 80 mg/day, 56% of patients on febuxostat 40 mg/day and 0% of patients randomized to placebo showed SU levels lower than 6 mg/dl [32]. However, the same group of patients on completing the study had SU levels lower than 5 mg/dl in 88, 49, 21 and 0% of patients randomized to febuxostat 120 mg/day, 80 mg/day, 40 mg/day and placebo, respectively. Moreover, 56% of patients randomized to febuxostat 120 mg/day had SU levels lower than 4 mg/dl [32].

Febuxostat was tested versus allopurinol in Phase III trials, one of which has been published [34]. A total of 762 patients with gout who showed no clinically significant renal function impairment were randomized in a 1:1:1 schedule to take allopurinol 300 mg/day or febuxostat 80 or 120 mg/day for 52 weeks. Baseline mean SU levels ranged from 9.80 to 9.90 mg/dl throughout the randomization groups, and the percentage of patients showing tophi in physical examination ranged from 23 to 26%. Mean body mass index was 32 kg/m^2 (over 60% of patients with obesity), 16% of patients had a history of previous urolithiasis, hypertension in 44%, hyperlipidemia in 34% and alcohol use was present in 66% of patients. Low-dose acetylsalicylic acid was used in 14–20% of the patients [34].

Serum urate levels lower than 6 mg/dl at the last 3-monthly visits was the primary outcome measure. The primary end point was achieved by 62, 53 and 21% of patients randomized to febuxostat 120 mg/day, febuxostat 80 mg/day, and allopurinol 300 mg/day, respectively. A SU level lower than 6 mg/dl at the final visit – a secondary end point – was achieved in 80, 74 and 36% of the patients randomized to febuxostat 120 mg/day, febuxostat 80 mg/day and allopurinol 300 mg/day, respectively [34].

Long-term follow-up studies have been reported only in abstract form to date [36,37]. The FOCUS trial of 116 patients is an extension, open-label, noncomparative titration study from Phase II that assigned patients to take febuxostat 80 mg/day, and allowed to titrate doses up to three times during the first 28-week follow-up period, to achieve and maintain SU levels in a range from 3 to 6 mg/dl [36]. At the time of the interim analysis, 53% had been exposed to febuxostat for at least 48 months. Tophi had resolved in 77% of patients showing a tophus on clinical examination at baseline, and flare rate decreased to less than or equal to one flare per patient-year after the first year of therapy, and nearly zero after the third year of therapy [36]. The dropout rate was 2–4% per year of follow-up, although personal reasons, consent withdrawal, noncompliance or SU over 6 mg/dl were the reasons for most withdrawals.

The EXCEL study included 735 patients coming from the Phase III trials, and compared the long-term efficacy and safety of febuxostat 80 mg/day, febuxostat 120 mg/day and allopurinol to a fixed dose of 300 mg/day in an open-label, randomized study, with a randomization ratio of 2:2:1, respectively [37]. Changes in urate-lowering therapy – alterations in the febuxostat doses or switching from febuxostat to allopurinol or from allopurinol to febuxostat – were allowed in the first 6-month follow-up period in order to attain SU levels from 3 to 6 mg/dl. Subjects failing to achieve SU levels lower that 6 mg/dl after adjustment of therapy at 6-month follow-up were considered to be therapeutic failures, and were withdrawn from the study. Overall, 22% of the patients initially randomized to febuxostat 80 mg/day, 29% to febuxostat 120 mg/day and 59% of patients randomized to allopurinol changed treatment for any reason. Failure to achieve the primary end point (SU < 6 mg/dl) was observed in 18% of patients assigned to febuxostat 80 mg/day, 8% of patients on febuxostat 120 mg/day and 57% of patients randomized to allopurinol 300 mg/day.

In addition, 67% of patients with failure to allopurinol 300 mg/day reached the primary end point when switching to febuxostat 80 mg/day or 120 mg/day if necessary.

Safety

In Phase III studies, patients were on colchicine or naproxen for the prophylaxis of acute episodes of inflammation for the first 8-week period of the trial. Results showed an increase of flares after prophylaxis therapy withdrawal, especially in patients with the lowest SU levels (the group receiving febuxostat 120 mg/day) [34].

Long-term safety was evaluated in the febuxostat Phase III trials and in the extension studies. At 52-week double-blind observation, adverse events were similar in the febuxostat 120 mg/day, febuxostat 80 mg/day and allopurinol 300 mg/day groups, and most adverse events were of mild-to-moderate severity [34]. The incidence of serious adverse events (SAEs) was similar in all three groups. More patients in the high-dose febuxostat group than in the allopurinol

group (p = 0.003) or the low-dose febuxostat group discontinued the study [34]. Withdrawal owing to abnormal liver function tests was more frequent in the febuxostat-treated patients. Four of the 507 patients in the two febuxostat groups (0.8%) and none of the 253 patients in the allopurinol group died; all deaths were from causes that the investigators (while still blinded to treatment) judged to be unrelated to the study drugs (p = 0.31 for the comparison between the combined febuxostat groups and the allopurinol group) [34]. In the EXCEL febuxostat extension study [37], SAEs were reported to be ten events per 100 patient-years for febuxostat and 11 per 100 patient-years for allopurinol. A third of the SAEs in each group were related to heart disorders, and all of them occurred in patients with previous cardiovascular history or cardiovascular risk factors [37].

Until more long-term safety data are available, 'treatment with febuxostat in patients with ischemic heart disease or congestive heart failure is not recommended' [101].

Clinical applicability

Whenever a new drug becomes available, the clinician would try to find the best place for such a tool in the therapeutic arsenal. Febuxostat may be useful for any patient with hyperuricemia and gout, but in some patients it may be of special interest.

Patients showing hyperuricemia in the highest range may be less prone to achieving the outcome of SU levels lower than 6 mg/dl [34,38] on standard doses of allopurinol. Indeed, even in patients with average SU levels at baseline, the average allopurinol dose required to achieve SU levels lower than 6 mg/dl was close to 400 mg/day [39]. Therefore, patients with the highest SU levels at baseline could be considered as candidates for highly effective urate-lowering therapy, either by increasing doses [39,40] or shifting to other available ULDs [38,41].

Patients with previous intolerance to allopurinol may have less therapeutic choices – namely, desensitization [42] for patients with mild cutaneous reactions, who should change to probenecid or benzbromarone [38,43], or use the mild uricosuric effect of other drugs if applicable when associated comorbidities allow prescription, such as fenofibrate for mixed hyperlipidemia [44].

In patients with significant renal function impairment, allopurinol dosing should be cautiously adjusted to avoid toxicity [45], an issue included in the EULAR recommendations for the treatment of gout [46]. Although higher than recommended doses [47,48], or adjusted doses up to 400–600 mg/day per dl of creatinine clearance may be prescribed without an increase in SAEs [49], a conservative approach may lead to poor control of hyperuricemia [50]. Patients with mild-to-moderate renal function impairment may benefit from prescription of drugs such as febuxostat or benzbromarone – the pharmacokinetics and efficacy of which are not substantially influenced by the presence of mild-to-moderate renal function impairment.

Another instance for considering highly effective ULDs [51] is in patients in whom a pronounced reduction of SU levels would be advisable in order to rapidly reduce the SU pool, such as patients with severe chronic tophaceous gout. Some studies suggest that in order to achieve rapid reduction of tophaceous monosodium urate deposition, the lower the SU levels are while undergoing therapy, the better the outcome [6,52–54].

Conclusion

Febuxostat is a new urate-lowering agent, specifically designed as a nonpurine inhibitor of XO. Its pharmacokinetic profile and clinical efficacy adds further possibility to the management of hyperuricemia of gout, especially in those patients in whom currently available drugs show unmet needs.

Future perspective

To date, studies of febuxostat have focused on chronic gout outcomes such as urate lowering, flare frequency and tophus regression. Although these are important end points for studies of chronic gout, a number of other outcomes should also be considered in patients with chronic gout [55]. These include health-related quality of life, pain, functional disability and work disability. The impact of febuxostat on joint damage is also unknown at present.

Recent investigations in animal models are exploring the efficacy of XO inhibitors on cardiovascular outcomes [56,57]. In a rabbit model, early treatment with febuxostat improved ventricular function after experimental coronary ligation [58].

In murine experimental models, treatment with febuxostat has been demonstrated to prevent renal injury both in the normouricemic and induced-hyperuricemic model [59]. Normalization of urate levels in a murine fructose-induced metabolic syndrome alleviated both metabolic and glomerular hemodynamics [59] and hypertension [60].

The clinical applicability of XO inhibition, either early or delayed, and through the use of either allopurinol or febuxostat, on cardiovascular and renal outcomes in humans – especially in

Executive summary

Mechanisms of action

- Febuxostat is a nonpurine inhibitor of xanthine-oxidase (XO).
- It displays a potent mixed-type inhibition of both oxidized and reduced forms of XO.

Pharmacokinetic properties

- Febuxostat has a bioavailablity of over 80% after oral administration.
- Bioavailability is minimally influenced by food.
- Febuxostat is mainly metabolized in the liver and excreted mainly as inactive metabolites by the kidneys, and through the bile ducts into the intestines.
- No clinically relevant interactions have been observed with thiazides, warfarin or NSAIDs.
- Mild-to-moderate renal or liver function impairment have not been shown to significantly influence the metabolism of febuxostat.

Clinical efficacy

- Febuxostat has been shown to be a potent urate-lowering agent in patients with hyperuricemia and gout, at 80–120 mg/day orally.
- Long-term extension studies support the sustained urate-lowering effect of febuxostat.
- The urate-lowering effect of febuxostat 80–120 mg/day is greater than that of allopurinol at 300 mg/day dosing.

Safety & tolerability

- Febuxostat is generally well tolerated and comparable in tolerability to allopurinol.
- Gout flares and increase in liver enzymes are the most commonly observed treatment-related side-effects.
- Potential safety concerns have been identified in regards to the cardiovascular safety of febuxostat, and caution should be taken until more studies are available.

Drug interactions

- Great caution should be put on concomitant administration of febuxostat and azathioprine, due to blockade of azathioprine metabolism.

relation to which groups of patients would benefit from such intervention, if any – has not yet been reported [61].

Financial & competing interests disclosure

Dr Perez-Ruiz has acted as a consultant for Ipsen, Savient, Pfizer and Ardea. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Bibliography

1. Mikuls TR, Saag KG: New insights into gout epidemiology. *Curr. Opin. Rheumatol.* 18, 199–203 (2006).
2. Yü TF, Gutman AB: Principles of current management of primary gout. *Am. J. Med. Sci.* 254, 893–907 (1967)
3. McCarthy G, Barthelemy CR, Veum JA, Wortmann RL: Influence of antihyperuricemic therapy on the clinical and radiographic progression of gout. *Arthritis Rheum.* 34(12), 1489–1494 (1991).
4. Yü TF: Milestones in the treatment of gout. *Am. J. Med.* 56, 676–685 (1974).
5. Zhang W, Doherty M, Bardin T *et al.*: EULAR evidence based recommendations for gout Part II. Management. Report of a Task Force of the EULAR Standing Committee for international clinical studies including therapeutics (ESCISIT). *Ann. Rheum. Dis.* 65, 1312–1324 (2006).
6. Perez-Ruiz F, Lioté F: Lowering serum uric acid levels: what is the optimal target for improving clinical outcomes in gout? *Arthritis Rheum.* 57(7), 1324–1328 (2007).
7. Sarawate AC, Patel PA, Schumacher HR, Yang W, Brewer KK, Baskt AW: Serum urate levels and gout flares. Analysis from managed care data. *J. Clin. Rheumatol.* 12, 61–65 (2006).
8. Riedel AA, Nelson M, Joseph-Ridge N, Wallace K, MacDonald PA, Becker M: Compliance with allopurinol therapy among managed care enrollees with gout: a retrospective analysis of administrative claims. *J. Rheumatol.* 31, 1575–1581 (2006).
9. Rundles RW, Metz EN, Silberman HR: Allopurinol in the treatment of gout. *Ann. Intern. Med.* 64(2), 229–258 (1966).
10. Gutman AB: Uricosuric drugs, with special reference to probenecid and sulfinpyazone. *Adv. Pharmacol.* 4, 91–142 (1966).
11. Sorensen LB, Levinson DJ: Clinical evaluation of benzbromarone. *Arthritis Rheum.* 19, 183–190 (1976).
12. Sherman MR, Saifer MGP, Perez-Ruiz F: PEG-uricase in the management of treatment-resistant gout and hyperuricemia. *Adv. Drug Deliv. Rev.* 60(1), 59–68 (2008).
13. Fukunari A, Okamoto K, Nishino T *et al.*: Y-700 [1-[3-Cyano-4-(2,2-dimethylpropoxy) phenyl]-1H-pyrazole-4-carboxylic acid]: a potent xanthine oxidoreductase inhibitor with hepatic excretion. *J. Pharmacol. Exp. Ther.* 311(2), 519–528 (2004).
14. Yeh L, Hingorani V, Manhard K *et al.*: Safety and uric acid lowering effect in humenas following multiple doses of RDEA806, a novel prodrug for the potential treatment of hyperuricemia. *Ann. Rheum. Dis.* 67(Suppl. II), 248–248 (2008).
15. Yeh L, Tamai I, Hamatake R *et al.*: Mode of action of RDEA594 as uric acid lowering agent in humans following multiple doses of its prodrug, RDEA806. *Ann. Rheum. Dis.* 67(Suppl. II), 247–247 (2008).
16. Takano Y, Hase-Aoki K, Horiuchi H *et al.*: Selectivity of febuxostat, a novel non-purine inhibitor of xanthine oxidase/xanthine dehydrogenase. *Life Sci.* 76(16), 1835–1847 (2005).

17. Okamoto K, Eger BT, Nishino T, Kondo S, Pai EF, Nishino T: An extremely potent inhibitor of xanthine oxidoreductase. Crystal structure of the enzyme-inhibitor complex and mechanism of inhibition. *J. Biol. Chem.* 278(3), 1848–1855 (2003).
18. Osada Y, Tsuchimoto M, Fukushima H *et al.*: Hypouricemic effect of the novel xanthine oxidase inhibitor, TEI-6720, in rodents. *Eur. J. Pharmacol.* 241(2–3), 183–188 (1993).
19. Komoriya K, Osada Y, Hasegawa M *et al.*: Hypouricemic effect of allopurinol and the novel xanthine oxidase inhibitor TEI-6720 in chimpanzees. *Eur. J. Pharmacol.* 250(3), 455–460 (1993).
20. Khosravan R, Grabowski B, Wu JT, Joseph-Ridge N, Vernillet L: Effect of food or antacid on pharmacokinetics and pharmacodynamics of febuxostat in healthy subjects. *Br. J. Clin. Pharmacol.* 65(3), 355–363 (2008).
21. Khosravan R, Grabowski BA, Wu JT, Joseph-Ridge N, Vernillet L: Pharmacokinetics, pharmacodynamics and safety of febuxostat, a non-purine selective inhibitor of xanthine oxidase, in a dose escalation study in healthy subjects. *Clin. Pharmacokinet.* 45(8), 821–841 (2006).
22. Khosravan R, Grabowski BA, Wu JT, Joseph-Ridge N, Vernillet L: Pharmacokinetics, pharmacodynamics and safety of febuxostat, a non-purine selective inhibitor of xanthine oxidase, in a dose escalation study in healthy subjects. *Clin. Pharmacokinet.* 45(8), 821–841 (2006).
23. Khosravan R, Grabowski B, Wu JT, Joseph-Ridge N, Vernillet L: Effect of food or antacid on pharmacokinetics and pharmacodynamics of febuxostat in healthy subjects. *Br. J. Clin. Pharmacol.* 65(3), 355–363 (2008).
24. Komoriya K, Hoshide S, Takeda K *et al.*: Pharmacokinetics and pharmacodynamics of febuxostat (TMX-67), a non-purine selective inhibitor of xanthine oxidase/xanthine dehydrogenase (NPSIXO) in patients with gout and/or hyperuricemia. *Nucleosides Nucleotides Nucleic Acids* 23(8–9), 1119–1122 (2004).
25. Khosravan R, Wu JT, Joseph-Ridge N, Vernillet L: Pharmacokinetic Interactions of Concomitant Administration of Febuxostat and NSAIDs. *J. Clin. Pharmacol.* 46(8), 855–866 (2006).
26. Mukoyoshi M, Nishimura S, Hoshide S *et al.*: *In vitro* drug-drug interaction studies with febuxostat, a novel non-purine selective inhibitor of xanthine oxidase: plasma protein binding, identification of metabolic enzymes and cytochrome P450 inhibition. *Xenobiotica* 38(5), 496–510 (2008).
27. Grabowski BA, Khosravan R, Wu JT, Lademacher C, Vernillet L: Effect of hydroclorthiazide on pharmacokinetics and pharmacodynamics of febuxostat. *Arthritis Rheum.* 52(Suppl.), S103–S104 (2005).
28. Hoshide S, Takahashi Y, Ishikawa T *et al.*: PK/PD and safety of a single dose of TMX-67 (febuxostat) in subjects with mild and moderate renal impairment. *Nucleosides Nucleotides Nucleic Acids* 23(8–9), 1117–1118 (2004).
29. Mayer MD, Khosravan R, Vernillet L, Wu JT, Joseph-Ridge N, Mulford DJ: Pharmacokinetics and pharmacodynamics of febuxostat, a new non-purine selective inhibitor of xanthine oxidase in subjects with renal impairment. *Am. J. Ther.* 12(1), 22–34 (2005).
30. Khosravan R, Grabowski BA, Mayer MD, Wu JT, Joseph-Ridge N, Vernillet L: The effect of mild and moderate hepatic impairment on pharmacokinetics, pharmacodynamics, and safety of febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase. *J. Clin. Pharmacol.* 46(1), 88–102 (2006).
31. Cummins D, Sekar M, Halil O, Banner N: Myelosuppression associated with azathioprineallopurinol interaction after heart and lung transplantation. *Transplantation* 61(11), 1161–1162 (1996).
32. Becker MA, Schumacher HR Jr, Wortmann RL *et al.*: 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.* 52(3), 916–923 (2005).
33. Becker MA, Kisicki J, Khosravan R *et al.*: Febuxostat (TMX-67), a novel, non-purine, selective inhibitor of xanthine oxidase, is safe and decreases serum urate in healthy volunteers. *Nucleosides Nucleotides Nucleic Acids* 23(8–9), 1111–1116 (2004).
34. Becker MA, Schumacher HR Jr, Wortmann RL *et al.*: Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N. Engl. J. Med.* 353(23), 2450–2461 (2005).
35. Schumacher HR, Becker MA, Wortmann RL *et al.*: Febuxostat vs. allopurinol and placebo in subjects with hyperuricemia and gout: the 28-week APEX study. *Arthritis Rheum.* 52(Suppl.), S680–S680 (2005).
36. Schumacher HR, Becker MA, Wortmann RL, Lloyd EJ, MacDonald PA, Joseph-Ridge N: The FOCUS trial 48-month interim analysis: long-term clinical outcomes of treatment with febuxostat in subjects with gout in an ongoing phase 2, open-label extension study. *Ann. Rheum. Dis.* 65(Suppl. II), 93–93 (2007).
37. Becker MA, Schumacher HR, MacDonald PA, Lloyd EJ, Lademacher C, Joseph-Ridge N: Urate-lowering therapy in subjects with gout: interim results from the febuxostat/allopurinol comparative extension long-term study (EXCEL). *Ann. Rheum. Dis.* 66 (Suppl. II), 230–230 (2007).
38. Perez-Ruiz F, Calabozo M, Fernandez-Lopez MJ *et al.*: Treatment of chronic gout in patients with renal function impairment. An open, randomized, actively controlled. *J. Clin. Rheumatol.* 5, 49–55 (1999).
39. Perez-Ruiz F, Alonso-Ruiz A, Calabozo M, Herrero-Beites A, Garcia-Erauskin G, Ruiz-Lucea E: Efficacy of allopurinol and benzbromarone for the control of hyperuricaemia. A pathogenic approach to the treatment of primary chronic gout. *Ann. Rheum. Dis.* 57(9), 545–549 (1998).
40. Reinders MK, Haggsma C, Jansen TL *et al.*: An randomized-controlled trial on the efficacy and tolerability with dose escalation of allopurinol 300–600 mg/day versus benzbromarone 100–200 mg/day in patients with gout. *Ann. Rheum. Dis.* doi:10.1136/ard.2008.091462 (2008).
41. Reinders MK, van Roon EN, Jansen TL *et al.*: Efficacy and tolerability of urate lowering drugs in gout: a randomised controlled trial of benzbromarone versus probenecid after failure of allopurinol. *Ann. Rheum. Dis.* DOI: 10.1136/ard.2007.083071, ard- (2008).
42. Fam AG, Dunne SM, Iazzetta J, Paton TW: Efficacy and safety of desensitization to allopurinol following cutaneous reactions. *Arthritis Rheum.*44(1), 231–238 (2001).
43. Grahame R, Simmonds HA, McBride MB, Marsh FP: How should we treat tophaceous gout in patients with allopurinol hypersensitivity? *Adv. Exp. Med. Biol.* 431, 19–23 (1998).
44. Hepburn AL, Kaye SA, Feher MD: Long-term remission from gout associated with fenofibrate therapy. *Clin. Rheumatol.* 22, 73–76 (2003).
45. Singer JZ, Wallace SL: The allopurinol hypersensitivity syndrome. Unnecesary morbility and mortality. *Arthritis Rheum.* 29(1), 82–87 (1986).
46. Zhang W, Doherty M, Bardin T *et al.*: EULAR evidence based recommendations for gout Part II. Management. Report of a Task Force of the EULAR Standing Committee for international clinical studies including therapeutics (ESCISIT). *Ann. Rheum. Dis.* 65, 1312–1324 (2006).
47. Vazquez-Mellado J, Meoño Morales E, Pacheco-Tena C, Burgos-Vargas R: Relation between adverse events associated with allopurinol and renal function in patients with gout. *Ann. Rheum. Dis.* 60, 981–983 (2001).
48. Panomvana D, Sriprdit S, Angthararak S: Higher therapeutic plasma oxypurinol concentrations might be required for gouty

patients with chronic kidney disease. *J. Clin. Rheumatol.* 14, 6–11 (2008).

49. Perez-Ruiz F, Hernando I, Villar I, Nolla JM: Correction of allopurinol dosing should be based on clearance of creatinine, but not plasma creatinine levels. Another insight to allopurinol-related toxicity. *J. Clin. Rheumatol.* 11, 129–133 (2005).
50. Dalbeth N, Stamp L: Allopurinol dosing in renal impairment: walking the tightrope between adequate urate lowering and adverse events. *Semin. Dial.* 20(5), 391–395 (2007).
51. Muñiz Caldas CA, Fuller R: Excellent response to the clinical treatment of tophaceous gout. *Clin. Rheumatol.* 26, 1553–1555 (2007).
52. Goldfarb E, Smythe CJ: Effects of allopurinol, a xanthine-oxidase inhibitor, and sulfinpyrazone upon the urinary and serum urate concentrations in eight patientswith tophaceous gout. *Arthritis Rheum.* 9(3), 414–423 (2007).
53. Perez-Ruiz F, Calabozo M, Pijoan JI, Herrero-Beites AM, Ruibal A: Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. *Arthritis Rheum.* 47(4), 356–360 (2002).
54. Perez-Ruiz F, Martin I, Canteli B: Ultrasonographic measurement of tophi as an outcome measure for chronic gout. *J. Rheumatol.* 34(9), 1888–1893 (2007).
55. Taylor WJ, Schumacher HR Jr, Singh JA, Grainger R, Dalbeth N: Assessment of outcome in clinical trials of gout a review of current measures. *Rheumatology* 46(12), 1751–1756 (2007).
56. Kanbay M, Ozkara A, Selcoki Y *et al.*: Effect of treatment of hyperuricemia with allopurinol on blood pressure, creatinine clearence, and proteinuria in patients with normal renal functions. *Int. Urol. Nephrol.* 39(4), 1227–1233 (2007).
57. George J, Carr E, Davies J, Belch JJF, Struthers A: High-dose allopurinol improves endothelial function by profoundly reducing vascular oxidative stress and not by lowering uric acid. *Circulation* 114(23), 2508–2516 (2006).
58. Zhao L, Roche BM, Wessale JL *et al.*: Chronic xanthine oxidase inhibition following myocardial infarction in rabbits: effects of early versus delayed treatment. *Life Sci.* 82(9–10), 495–502 (2008).
59. Sanchez-Lozada LG, Tapia E, Bautista-Garcia P *et al.*: Effects of febuxostat on metabolic and renal alterations in rats with fructose-induced metabolic syndrome. *Am. J. Physiol. Renal Physiol.* 294(4), F710–F718 (2008).
60. Sanchez-Lozada LG, Tapia E, Soto V *et al.*: Treatment with the xanthine oxidase inhibitor febuxostat lowers uric acid and alleviates systemic and glomerular hypertension in experimental hyperuricaemia. *Nephrol. Dial. Transplant.* 23(4), 1179–1185 (2008).
61. Strozzullo P, Puig JG: Uric acid and cardiovascular risk: Is the devil always so bad? *Nutr. Metab. Cardiovasc. Dis.* 17(6), 409–414 (2007).

Website

101. European Medicines Agency. EPACHMP assessment report for Adenuric (2008). www.emea.europa.eu/humandocs/PDFs/EPAR/adenuric/H-777-en6.pdf

Affiliations

- Fernando Perez-Ruiz, MD, PhD
Rheumatology Division, Hospital de Cruces, Pza Cruces sn, 48903 Baracaldo, Vizcaya, Spain
Tel.: +34 946 006 470
Fax: +34 944 905 985
fernando.perezruiz@osakidetza.net
- Nicola Dalbeth, MD, FRACP
Department of Medicine, University of Auckland, Auckland, New Zealand
- Naomi Schlesinger, MD
Division of Rheumatology, Department of Medicine, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, USA