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REVIEW ARTICLE

International position paper on febuxostat

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Abstract This position paper aims to clarify the presumed place of febuxostat in the management of gout patients. Since this novel xanthine oxidase inhibitor is now available, an international group of gout experts decided to formulate an international consensus statement. This statement presents the place for this new xanthine oxidase inhibitor in the treatment of gout which may contribute to optimize treatment of gout patients in Europe and worldwide.

Keywords Allopurinol · Febuxostat · Gout · Urate-lowering therapy · Uricosuric · Xanthine-oxidase inhibitor

Aim

This position paper aims to clarify the presumed place of febuxostat in the management of gout patients. Since this

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novel xanthine oxidase inhibitor is now available as a new treatment option for patients with gout, an international group of gout experts decided to formulate a rheumatologic international consensus statement. This statement presents the place for this new xanthine oxidase inhibitor in the treatment of gout which may contribute to optimize treatment of gout patients in Europe and worldwide.

Introduction

Gout affects 1–2% of adults. It is the most common inflammatory arthritis in developed countries and can be considered as a curable metabolic disorder [1]. Clinically, gout may manifest with acute attacks of arthritis or with tophaceous accumulation of sodium urate. Identification of negatively birefringent needles of sodium urate by polarizing microscopy is considered the gold standard for the diagnosis of gout. Indications for urate-lowering therapy (ULT) in gout include frequent acute attacks, tophaceous accumulation, gouty joint damage and urolithiasis. ULT aims to prevent the formation of new crystals and to dissolve existing urate crystals by reducing urate levels below the critical saturation point for urate crystal formation. Currently licensed ULT options comprise uricosurics and/or xanthine oxidase inhibitors (XOI) [2–4]. Allopurinol is a purine, non-selective XOI which is generally available in all countries. Uricosuric agents, including benzbromarone, probenecid and sulfinpyrazone, have more limited availability in Europe. This lack of alternative treatment options contributes to the suboptimal treatment of gout [5]. Recently, a novel non-purine highly selective XOI, febuxostat, has emerged as a potential alternative to allopurinol. Febuxostat 80 to 120 mg daily has been approved for the treatment of clinical manifestations associated with hyperuricaemia by the European Medicines Agency (EMEA) for its use in Europe [6].

Current options in urate-lowering treatment

Allopurinol, a pyrazolopyrimidine and analogue of hypoxanthine, is widely prescribed as the ULT of first choice. Allopurinol has been proven to be effective in all cases of hyperuricaemia. The active metabolite of allopurinol, oxipurinol, is excreted via the kidney and has a long half-life (about 14–28 h), allowing allopurinol to be administered once daily. Although allopurinol is often prescribed at a fixed dose of 300 mg daily, recent guidelines recommend individualized treatment based on serum uric acid (SUA) and creatinine clearance, with upward titration of allopurinol dosage against SUA levels until the therapeutic target has been achieved. A 6-month prophylaxis with low-dose colchicine or non-steroidal anti-inflammatory drug (NSAID) is recommended by the EMEA and European League Against Rheumatism (EULAR) [3, 7]. The target recommended by EULAR is <360 μmol/l (EULAR target) although the target recommended in the UK is more stringent (<300 μmol/l) [3, 4]. The lower the SUA below 360 μmol/l, the faster the velocity of tophus reduction and the sooner the cessation of further acute attacks [7]. Commonly, one starts with 100 mg allopurinol daily, with incremental increases of 100 mg daily every 2–4 weeks until the therapeutic target is reached. For some patients, a daily dose of 100 mg allopurinol may be adequate, but for many, the requirement is 300–500 mg daily. The highest recommended dose of allopurinol varies between countries but may be as high as 600–900 mg daily. In Dutch studies, a daily dosage of 300 mg allopurinol lowered SUA to below the EULAR target (<360 μmol/l) in 56–65% of patients and to <300 μmol/l (the British target) in 20–26% of cases [8, 9], whereas the higher daily dosage of 600 mg reached these targets in 93% and 78% of patients, respectively [9]. Approximately 20% of patients using allopurinol reports adverse events, with 5% discontinuing its use [1]. The allopurinol hypersensitivity syndrome or drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is rare but life-threatening. Serious adverse reactions to allopurinol have been related to daily dose and decreased creatinine clearance rate with secondary prolonged half-life of oxipurinol, and therefore, it was proposed by Handle et al. in 1984 to adjust the allopurinol dose according to renal function.

For patients with minor allopurinol allergy (e.g. skin rash without systemic upset) desensitization may be attempted, with expected success in ~50% of cases; however, desensitization should not be tried in those with DRESS syndrome. For patients who are intolerant of allopurinol, urocosurics may be considered as an alternative ULT strategy. In recent randomized controlled trials (RCTs), benzbromarone 100–200 mg daily showed a higher success rate than probenecid 1,000 mg daily, but a similar success rate when compared with allopurinol 300–600 mg daily [8, 9]. However, because of concerns over reports of rare hepatotoxicity (some serious), benzbromarone was taken off the European market in 2003, to be later reintroduced in some countries with a restricted license for patients intolerant of allopurinol. Probenecid and sulphinpyrazone are contraindicated in patients with renal impairment due to inefficiency in lowering SUA and risk of uric acid nephrolithiasis with worsening of renal function. Benzbromarone, however, remains efficient and apparently safe in patients with mild-to-moderate renal impairment (Table 1).

Table 1 Percentage of patients reaching target as mentioned in left box at final study visit [8–10]

SUA <300 µmol/l	Allopurinol 300: 24–26% [8, 9], 13% [10]	Febuxostat 80: 47–49% [10, 12]	Febuxostat 120: 66–88% [10, 12]
SUA <360 µmol/l	Allopurinol 300: 56–65% [8, 9], 36% [10]	Febuxostat 80: 74–76% [10, 12]	Febuxostat 120: 80–94% [10, 12]

Febuxostat

This is a non-purine drug designated as 2-[3-cyano-4-(2-methylpropoxy) phenyl]-4-methlythiazole-5-carboxylic acid. In Europe, it is available in two doses, 80 or 120 mg.

Reviewing the data, febuxostat can be regarded as a useful novel non-purine, selective XOI that does not interfere with other enzymes in the purine/pyrimidine pathways. Pharmacokinetic studies show that febuxostat 10–120 mg daily behaves linearly (see http://www.ema.europa.eu/humandocs/PDFs/EPAR/adenuric/H-777). Febuxostat is metabolized and excreted by the liver, so no dose adjustment appears to be necessary in patients with mild-to-moderate renal impairment (creatinine clearance >30 ml/min) or mild-to-moderate hepatic impairment. As pharmacokinetics and pharmacodynamics of febuxostat are not substantially affected by age or gender; therefore, dose adjustment is not required based on these data. Regarding non-Caucasian ethnic groups, no definite conclusions can be drawn due to the small number of patients from a non-Caucasian descent.

Pivotal trials of febuxostat are summarized in the attachment.

Because both 80 and 120 mg of febuxostat are efficient at lowering SUA, initiation of treatment can provoke acute attacks of gout. A 6-month prophylaxis with colchicine or if possible a shorter course of NSAID is recommended [6]. A disadvantage of febuxostat is that it is available in only two recommended doses and the tablets are not readily divisible, providing little opportunity to slowly titrate up the daily dose. In general, febuxostat is well tolerated in clinical trials. However, some concerns were raised regarding the elevation of liver enzymes in 3–5% of patients and a non-significant but higher rate of death and cardiovascular events on febuxostat compared to allopurinol 300 mg. This led to an EMEA restriction on the use of febuxostat in patients with severe cardiovascular disease.

Febuxostat 80 mg daily appears more effective than allopurinol 300 mg in lowering SUA but may be less effective than allopurinol 600 mg daily. Although a direct comparison is not available, in American patients, the target SUA of <360 µmol/l is reached in 53% of those on febuxostat 80 mg/day and only 21% of those on allopurinol 300 mg/day, whereas in Dutch patients, this therapeutic target is achieved in 56–65% of those taking allopurinol 300 mg/day and 85% of those on allopurinol 600 mg/day (see Table 2) [8–11]. In studies of US patients, the lower target SUA of <300 µmol/l is reached in 47–49% of patients on febuxostat 80 mg/day versus 13% of those on allopurinol 300 mg/day, whereas in studies within Europe, this target is achieved in about 25% of patients on allopurinol 300 mg/day and fully 78% (confidence interval 59–89%) of those on allopurinol 600 mg/day [8–10, 12]. These differences in therapeutic success in studies of North Americans compared to Europeans may be explained by different dietary habits (related to purine/fructose/alcohol intake), greater severity of the disease as well as higher body mass indices in North Americans.

Indications and contraindications

Based upon currently available data on efficacy, safety and cost, our recommendation is that febuxostat should *not be considered as first-line ULT* in patients with gout and associated hyperuricaemia. Indeed, this has been stated explicitly by the National Institute for Clinical Excellence in the UK (see http://www.nice.org.uk/nicemedia/pdf/TA164Guidance.pdf). However, febuxostat might be considered as appropriate ULT to try in patients with hyperuricaemia and gout in the following circumstances:

Indications:

1. In patients with gout who are intolerant of allopurinol and who have failed, or who have contraindications for available uricosuric ULT. (Caution—when febuxostat is initiated in patients with allopurinol-associated allergy, close monitoring is advised. Currently, data are lacking concerning cross-allergy, although the differences of

Table 2 Potency indicating percentage of patients (caveat: patients from USA versus Dutch cohorts) reaching the target of SUA <0.30 mmol/l [8–12]

	European RCTs [8, 9] (%)	USA RCTs [10–12] (%)
Allopurinol 100 mg/day	nd	0
Allopurinol 300 mg/day	24–26 [8, 9]	13 [10]
Febuxostat 40 mg/day	nd	21 [12]
Febuxostat 80 mg/day	nd	47–49 [10, 12]
Allopurinol 600 mg/day	78 [9]	nd
Febuxostat 120 mg/day	nd	66–88 [10, 12]
Febuxostat 240 mg/day	nd	>69 [11]

nd not done

chemical structures between febuxostat and allopurinol make this unlikely.)
2. In patients who do not achieve the therapeutic target on allopurinol at the highest dosage recommended, at the highest dose that they can tolerate (due to upset at higher doses) or at the highest dose that is individually indicated (due to chronic renal impairment and/or potential toxicity).

Contraindications are:

1. Intolerance to febuxostat such as development of one of the serious adverse events,
2. Moderate to severe non-alcoholic hepatic impairment (transpeptidases >3 times the upper limit of normal or Child–Pugh score >9 taking into account: bilirubin, INR, albumin, presence of ascites and encephalopathy),
3. Xanthine-associated side effects (rare: xanthinosis, etc.),
4. Patients requiring azathioprine: febuxostat may well influence the metabolism of azathioprine and 6-mercaptopurine, as does allopurinol. Caution, with reduction in azathioprine dosage, is recommended in cases with concomitant administration,
5. Pregnancy or women of child-bearing age with inadequate contraception,
6. Caution is recommended in patients with ischaemic heart disease or severe congestive heart failure.
7. Severe renal failure (creatinine clearance <30 ml/min): In patients with creatinine clearance <30 ml/min but >20 ml/min, a lower initial dose of 40 mg febuxostat could be considered. However, in Europe, only 80 and 120 mg febuxostat tablets will be available.

Recommended monitoring

Before prescribing febuxostat:

1. Documentation of allopurinol intolerance/refractoriness/contraindication.
2. Full blood count (FBC); transpeptidases aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT); albumin; thyroid-stimulating hormone (TSH); creatinine; SUA; creatinine clearance.
3. Prophylaxis using colchicine in appropriate dosage or alternatively an NSAID at low dose at least 3 days before starting febuxostat. Caveat: long-term NSAIDs.

During therapy:

1. After 2–4 weeks: FBC; serum creatinine; SUA; ALAT and/or ASAT (24-h urate and creatinine clearance particularly if a uricosuric is considered).
2. After 12 weeks and every 8 weeks thereafter: FBC; creatinine; urate; ALAT and/or ASAT (24-h urate and creatinine clearance particularly if a uricosuric is considered).
3. After 6 months and every 6 months thereafter TSH; how useful this advice is remains to be seen.
4. SUA target according to EULAR: <0.36 mmol/l.
5. If SUA target <0.36 mmol/l cannot be reached by administering febuxostat 80 mg/day as a starting dose nor by subsequent increase in febuxostat to120 mg daily, consider the addition of one of the uricosurics if these are not contraindicated (although currently no data are available on such combination therapy).
6. If the therapeutic target is not achieved by febuxostat up to the maximum recommended dose (120 mg daily if tolerated) or by febuxostat plus a uricosuric, then febuxostat should be discontinued within a 3-month period and alternative ULT considered.

Research agenda

Several areas with unclosed issues remain. In phase IV studies, a number of gaps in our current knowledge should be addressed. The most important issues are:

1. Appropriate dose titration in renal impairment,
2. Safety and tolerability of febuxostat in gout patients with allopurinol-associated intolerance or side effects,
3. Efficacy (success in achieving the therapeutic target with subsequent reduction in tophi and attack frequency) and safety of combination therapy with a uricosuric (e.g. benzbromarone) for those patients who do not achieve the therapeutic target with febuxostat alone,
4. Specific pharmacovigilance is warranted regarding haematological and hepatic effects, as well as thyroid function,
5. Monitoring of febuxostat tolerance in phase IV, i.e. clinical practice,
6. Cardiovascular safety: already committed to be a major topic in phase IV studies,
7. Safety profile after large exposure to the drug. If no rare but severe SAE including DRESS is recorded, febuxostat could become an alternative to allopurinol when initiating ULT.

Conclusion

Febuxostat emerges as an important new therapeutic option in gout. Presently, febuxostat cannot be considered as first-

line therapy, but only after treatment failure of allopurinol. Flare prophylaxis is required with febuxostat according to the EULAR guidelines. Daily dosing and titration of febuxostat needs to be individualized in order to reach EULAR targets.

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Appendix

Attachment 1: pivotal clinical efficacy studies of febuxostat and side effects

Becker et al. randomly assigned 762 patients with gout and with serum urate concentrations of at least 8.0 mg/dl (480 μmol/l) to receive either febuxostat (80 or 120 mg) or allopurinol (300 mg) once daily for 52 weeks; 760 patients received the study drug [10]. Prophylaxis against gout flares with naproxen or colchicine was provided during weeks 1 through 8. The primary endpoint was a target SUA <6.0 mg/dl (360 μmol/l) at the last three monthly measurements. The secondary endpoints included reduction in the incidence of gout flares and in tophus area. The primary endpoint was reached in 47–59% of patients receiving 80 mg of febuxostat, 44–74% of those receiving 120 mg of febuxostat and 8–40% of those receiving 300 mg allopurinol ($P<0.001$ for comparison of each febuxostat group with the allopurinol group). Febuxostat was concluded, at a daily dose of 80 or 120 mg, to be more effective than 300 mg allopurinol in lowering SUA. Similar reductions in gout flares and tophus area occurred in all treatment groups (Table 1).

Schumacher et al. randomly assigned 1,072 patients with gout, including persons with impaired renal function, and with SUA concentrations of at least 8.0 mg/dl (480 μmol/l) to receive either febuxostat (80, 120 or 240 mg) versus allopurinol (300 or 100 mg) once daily for 28 weeks versus placebo [11]; significantly higher percentages of subjects treated with febuxostat 80 mg (48%), 120 mg (65%) and 240 mg (69%) attained the primary endpoint of at least three monthly SUA levels <6.0 mg/dl (360 μmol/l) compared with allopurinol (22%) and placebo (0%). A significantly higher percentage of patients with impaired renal function treated with febuxostat 80 mg (4 out of 9=44%), 120 mg (5 out of 11=45%) and 240 mg (3 out of 5=60%) achieved the primary endpoint compared with those treated with 100 mg allopurinol (0 out of 10=0%).

Serious adverse events occurred similarly in all groups, although diarrhea and dizziness were more frequent in the 240-mg febuxostat group. Primary reasons for withdrawal were similar across groups except for gout flares, which occurred more frequent with febuxostat than with allopurinol. Schumacher et al. concluded that, at all doses studied, febuxostat more effectively lowered and maintained serum urate levels below 6.0 mg/dl (360 μmol/l) than allopurinol or placebo did in subjects with hyperuricaemia and gout, including in those with mild-to-moderate impaired renal function [11]. Becker et al. randomly assigned 153 patients in a phase II RCT, including patients aged 23 up to 80 years, to receive either febuxostat 40 versus 80 versus 120 mg or placebo once daily for 28 days with colchicine prophylaxis [12]. SUA concentrations reached levels below 360 μmol/l in 56% versus 76% versus 94% versus 0% in respective febuxostat dosages. SUA below 300 μmol/l was reached in, respectively, 21%, 49%, 88% and 0%. The authors thus concluded that febuxostat is effective, well tolerated and safe for the short-term treatment. For the last two conclusions, we now have a 5-year open-label extension study, including 116 patients after the 28-day double-blind study (with only 58 completers) [13]. Febuxostat resulted in a durable maintenance of SUA below 360 μmol/l for most subjects. This was associated with nearly complete abolition of gout flares and resolving tophi in the majority of patients at the cost of some side effects [13], see Table 2. In the long-term study, 13 out of 116 (11%) reported an adverse event as primary reason for premature discontinuation. The most common adverse events leading to withdrawal were abnormal liver function tests ($n=3$), cancer ($n=3$) and increase serum creatinine ($n=2$). These abnormalities resolved within 10–106 days, and the three abnormal liver function tests and one of the renal dysfunction were considered to be related with study drug treatment, though alcohol abuse was not fully excluded in two out of three liver function abnormalities. The long-term study, however, had a flaw in design as it started with a selection bias, including preferentially responsive and

compliant and febuxostat was well tolerated by all patients.

Attachment 2

It is strongly advised to report serious adverse events to local authorities. Adverse events in the 5-year follow-up study [13]:

Most frequently reported adverse events	In 116 subjects	Percentage
Upper respiratory tract infection	51	53
Locomotor complaints	42	36
Joint-related signs/symptoms	33	28
Diarrhea	24	21
Influenza	20	17
Headache	18	16
Par/dysaesthesia	16	14
Lower respiratory tract infections	15	13
Liver function analyses	15	13
Vascular hypertensive disorders	15	13
Gastrointestinal/abdominal complaints	14	12
Rash/eruption/exanthema	14	12
Oedema	12	10
Pain and discomfort	12	10
Tendon disorders	12	10
Serious adverse events		
Subjects with at least one serious event	21	18
AV block or atrial fibrillation	6	5
Small intestinal obstruction/diverticular or appendicular perforation	3	3
Non-cardiac chest pain	1	<1
Cholecystitis	2	2
Infections/infestations	4	3
Concussion/traumatic fracture/excoriation	3	3
Intervertebral disc degeneration/rotator cuff syndrome/osteoporosis fracture	5	4
Neoplasm	4	3
Alzheimer/cerebrovascular accident	2	2
Depression	1	<1
Urinary retention	1	<1

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