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REVIEW ARTICLE

International position paper on the appropriate use of uricosurics with the introduction of lesinurad

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Abstract

Over the last 70 years, pharmacotherapy in gout with urate-lowering drugs has consisted of four drugs only: In 1952, a mild uricosuric probenecid became available, the xanthine oxidase inhibitor Allopurinol in 1964, and the latter became the most frequently used urate-lowering drug worldwide; in the Eurozone, the uricosuric benzbromarone was welcomed in 1977. Only in 2002, the potent non-purine xanthine oxidase inhibitor febuxostat was introduced. In many countries, uricosurics such as probenecid and benzbromarone have not been available up to now, and these days, the new uricosuric lesinurad is the first uricosuric that may be introduced in these countries, which is the reason for describing the position this novel uricosuric deserves in treating gout. Recent literature will be shortly reviewed, and the current proposed position for lesinurad will be given as an aid for clinicians.

Keywords Benzbromarone · Gout · Lesinurad · Urate-lowering therapy · Uricosuric

Introduction

Gout is the most common arthritic disease in which recurrent (auto-) inflammatory episodes are driven by arousal of the inflammasome due to deposited monosodium urate (MSU) crystals.

These urate depositions are to be considered as proof for a metabolic disorder resulting in long-standing hyperuricemia due to a positive urate balance which is commonly in day-to-day clinical practice evaluated by measuring a high serum urate level [1]. Once this diagnosis in a patient has been made, ideally by performing a puncture with the detection of MSU crystals by (polarized) light microscopy, individualized therapeutic targets of lowering the serum urate (SUA) levels will be aimed for, a so-called treat-to-target strategy according to EULAR recommendations: in uncomplicated gout as MTP1 arthritis (podagra) SUA level < 0.36 mM (< 6 mg/dL), and even < 0.30 mM (< 5 mg/dL) if the patient suffers from severe gout (e.g., polyarticular, tophaceous) [2]. Patient education and patient empowerment are of major importance in the first instance as they have been shown to be essential for adequate adherence of the patient [3].

Next to urate-limiting diets, three urate-lowering strategies are available for this treatment: urate production inhibitors (XOi = xanthine oxidase inhibitors) as well as uricosurics (US), and uricolytic uricases; see Fig. 1.

As during the first month of the initiation of urate-lowering therapy, the incidence of gout flares is higher—explained by "debulking" of urate crystal deposits with so-called mobilization flares—there is need of an effective gout flare

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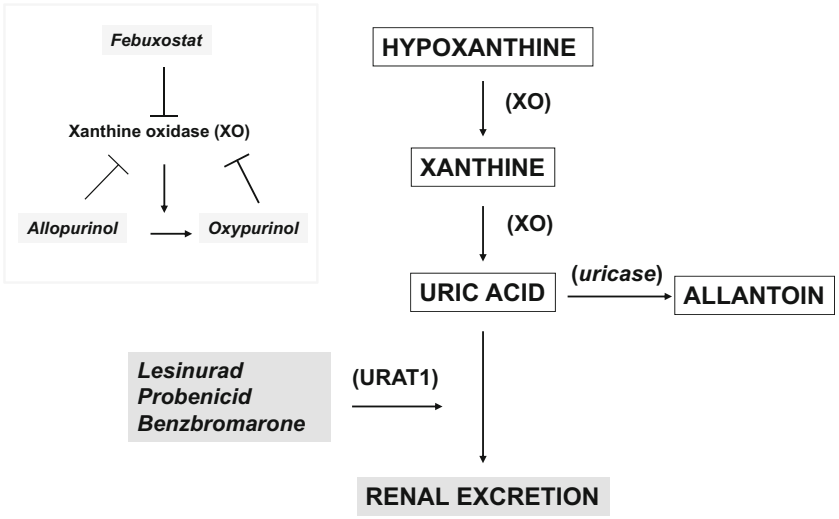

Fig. 1 Urate-lowering strategies

prophylaxis. Covered by effective gout flare prophylaxis, urate-lowering therapy as the rational pharmacotherapy of gout should be started at low dose and up-titrated if needed to reach the prespecified target of 0.36 mM (6 mg/dL) or 0.30 mM (5 mg/dL) according to the patient's phenotype (see EULAR recommendations) to effectively reach the clinical and/or biochemical target as soon as possible. For this aim, there are the following drugs available in Europe (Table 1).

Reduced renal excretion of urate plays a pivotal role in the development of hyperuricemia. In about 90% of all gout patients, a lower urate excretion is causative [1, 2]. Despite this high occurrence of the low urate excretors, a purine diet combined with a xanthine oxidase inhibitor is the first choice option due to proven efficacy and safety in general: allopurinol, or in case of allopurinol intolerance, febuxostat. Individualized dosing and targeting is here of major importance: Allopurinol dose should be started at low dose (e.g., 100 mg/day), slowly up-titrated and escalated up until the predefined serum target has been reached [2]. If the urate serum target cannot be reached or intolerance occurs, one has to consider intensified treatment or switch to febuxostat or the combination of two modes of action (MoA): XOi PLUS a uricosuric to intensify the urate excretion. This combined action is very potent in reducing the serum urate and getting a negative urate balance for rapid resolution of urate deposits [2].

Renal factors are significant contributors to the increased serum urate values: reduced glomerular filtration rate (GFR), medication-induced increase in renal urate reabsorption, or a modulatory role on the renal urate transporters: URAT1, OAT1/OAT3/OAT4, see Table 2 [1, 3, 4].

Table 1 Drugs available in Europe

Allopurinol (XOi)	100–800 mg QD	First choice option, if no intolerance/allergy coexists Caveat hypersensitivity: Be careful * During first 6 months (90ste percentile of hypersensitivity reactions) * HLA B*5801 * High initial doses * Renal insufficiency/failure
Febuxostat (XOi)	80–120 mg QD	After allopurinol * If target is not reached * If contraindicated/not tolerated Might be preferable in higher stages of renal impairment
Benzbromarone (US) Available in Germany, The Netherlands, Spain	50–100 mg QD	After failure of monotherapy allopurinol/febuxostat, and only approved in monotherapy so not in combination with a XOi except for Germany where combined use is approved (Allo comp consisting of 20 mg benzbromarone)
Lesinurad (US) Currently available in Austria, Italy, and Switzerland, and procedures have started in the others	200 mg QD	After failure of first choice option in XOi monotherapy and *only approved in* combination with a XOi

XOi xanthine oxidase inhibitor, *US* uricosuric, *QD* (quaque die) once daily, *BID* (bis in die) twice daily, *TID* (tres in die) three times daily, *QID* (quarter in die) four times daily

Table 2 Uricosurics labeled as urate-lowering therapy in gout in the European Union

Medication	MOA	Relevant features
Probenecid 500 mg–1 g QD	Inhibitor URAT1 Inhibitor OAT1/OAT3	Common drug-to-drug interactions; loss of effect in moderate to severe CKD
Benzbromarone 100–200 mg QD	Inhibitor URAT1	Mitochondrial toxicity sporadically elevation of liver function tests; unfrequently even liver failure
Lesinurad 200 mg QD	Inhibitor URAT1 Inhibitor OAT4	No clinically relevant PK; plasma transient creatinine elevations

MOA mode of action, *PK* pharmacokinetics, *CKD* chronic kidney disease

Uricosurics in historical perspective

Inducing a higher urate excretion has been tried before but appeared to be not without incidents on these occasions: Severe renal toxicity was seen with the uricosuric Tienilic acid/Ticrynafen due to idiosyncrasy and hypersensitivity, i.e., hepatitis based on microsomal antibodies type 2 [5] and PF-06743649, a dual inhibitor of XO and URAT1 showing acute kidney injury episodes in healthy subjects and subsequently withdrawn from further development [6].

Initially, benzbromarone was granted by all European authorities. Benzbromarone, however, was associated with fatal liver toxicity in sporadic cases; it was these serious adverse events that prompted the licensing pharmaceutical company to withdraw benzbromarone from the market in most European countries [7]. Therefore, the study data of lesinurad, a novel uricosuric agent, was of interest. Unfortunately, with lesinurad monotherapy, serum creatinine increases of unknown origin, and renal side effects occurred in a significant percentage and thus prompted AstraZeneca to stop for market authorization of monotherapy lesinurad 400 mg [8]. Even in case of intolerance to XOi lesinurad 400 mg, monotherapy is contraindicated as renal "adverse events" (AE) occurred in 18% and serious AE in 4.7% with a serum creatinine increase (factor 1.5× increase) [8]. As an add-on to XOi, the uricosuric lesinurad 200 mg has shown to be safe and effective in lowering urate levels to target and has been approved by the EMA. Another potent uricosuric Verinurad is under investigation still and waiting for further clinical development.

Effectiveness

Lesinurad is quite a potent uricosuric as it effectively may help reaching the serum urate target below 0.36 mM (6 mg/dL) in gout patients, and even the target of 0.30 mM (5 mg/dL) whichever is the individualized target to aim for; see Fig. 1. Dalbeth et al. demonstrated in the CRYSTAL study (which included severe diseased gout patients with tophi) that febuxostat monotherapy may help at reaching the target of serum urate below 0.30 mM in 41% and if using combination therapy in 57% of gout patients after 12 months of treatment [9].

Saag et al. showed in the CLEAR-1 study that these percentages were 10% with allopurinol 300 mg QD monotherapy versus 29% allopurinol/lesinurad combination therapy, and Bardin et al. showed in CLEAR-2 study 5% and 35%, respectively [10, 11]. Pooled post hoc analysis of the CLEAR studies showed that for patients using concomitant thiazide or thiazide-like diuretics (TTLDs), the allopurinol/lesinurad combination has a similar efficacy and safety as the group not using such diuretics. This is of special interest because TTLDs are widely used for the treatment of arterial hypertension which is a predominant comorbidity in gout patients. TTLDs per se are known to reduce the urate excretion which is the presumed cause for the increased incidence of gout in these patients [12].

Statement

Efficacy	Lesinurad 200 mg QD is effective as add-on therapy with allopurinol 300 mg daily as one in three patients reached < 0.30 mM as target Lesinurad combined with XOi allopurinol may be considered safe during the first 2 years
Efficacy	Lesinurad 200 mg QD is effective as add-on with febuxostat 80 mg daily as two in three gout patient reached< 0.30 mM as target Lesinurad combined with XOi febuxostat may be considered safe during the first 2 years

Safety

No major concerns regarding safety were met, but some considerations are mentioned regarding EU label:

1. Lesinurad 200 mg QD only to be used in combination therapy with XOi and to be withdrawn if XOi is stopped

2. Renal function to be tested prior to and regularly during treatment
3. Not to be recommended in patients with a recent cardiovascular event

Statement

Safety	Lesinurad combined with the XOi allopurinol/febuxostat may be considered safe during the first 2 years

Safe use of uricosurics in day-to-day practice may only be reached if fluid intake is adequate. Increasing the urate excretion may result in severe sequelae once there is a dehydration, as this dehydration state may easily result in a urinary acidosis which enhances stone formation of urate postrenally: in calyces and urinary tract.

Interactions

Consider some C2A9 interaction (such as in patients who need only very low doses of acenocoumarol or warfarin; this may occur in one out of six patients in some populations). Some other interactions have been studied such as those with nonsteroidal anti-inflammatory drugs (NSAIDs), naproxen, and indomethacin in particular [13–15].

- The uricosuric effect may be impaired with the combined use of naproxen: AUC (area under the curve) of lesinurad was − 27% reduced, but interestingly, this was not the case with combined use of indomethacin (AUC was reduced with 0%) [13].
- The analgesic effect of indomethacin may be reduced with lesinurad as the AUC was reduced with − 35%, versus with colchicine − 25%, versus 0% reduction of AUC with the simultaneous application of naproxen [13].

Statement

Efficacy as a uricosuric	The uricosuric effect of lesinurad may be diminished with the combined use of naproxen but not with indomethacin PLUS lesinurad
Interaction	The analgesic effect may be diminished with the combined use of indomethacin and possibly colchicine, but not with naproxen PLUS lesinurad

Indication for lesinurad

Lesinurad 200 mg QD is a uricosuric; one may need to consider as an add-on-therapy if the individual serum urate target cannot be reached with the application of a xanthine oxidase inhibitor in the maximal tolerated dose. The effectivity of lesinurad, however, may be reduced when glomerular filtration rate (GFR) is below 30–45 mL/min; therefore, it is not recommended in patients with GFR < 30 (EU label) or GFR < 45 mL/min (FDA label) (http://www.ema.europa.eu/docs/enGB/documentlibrary/EPAR-ProductInformation/human/003932/WC500203066.pdf).

EMA registration

Lesinurad 200 mg has been centrally registered for the European Union but only for the combination therapy with either allopurinol 200–300 mg/day or febuxostat (without specific dose). Prior to the add-on of lesinurad in most countries, clinicians are allowed by label to escalate the allopurinol dose individually if tolerated up to 600 mg daily, sporadically even up to 900 mg daily, but long-term safety data are so far not available. Monotherapy with lesinurad is with regard to current available data contraindicated due to an increased renal risk.

Two dual pills containing a fixed dose of allopurinol 200 mg or 300 mg/day plus lesinurad 200 mg/day as been recently approved for the EU (http://www.ema.europa.eu/docs/enGB/document_library/EPAR-ProductInformation/human/004412/WC500254466.pdf).

Dosing

In the pivotal trials, 2 additional doses have been studies: 400mg and 600mg Lesinurad. Already at 400mg Lesinurad monotherapy in the LIGHT study has shown relevant renal side effects—increase in serum creatinine and loss in renal function in 30% with an ultimate stop, i.e., drop-out of study in 33% versus only 2% in placebo arm [8]. In the combination studies with a XOi, the CRYSTAL, CLEAR1, and CLEAR2 study, the lesinurad 200 mg dose turned out to be safe in the combination with febuxostat (CRYSTAL) and allopurinol (CLEAR). The 0.30 mM serum target was obtained in 57% with febuxostat (CRYSTAL) and 29–35% with allopurinol (CLEAR1/CLEAR2) [9–11].

In common daily practice, one may first try to escalate the allopurinol exceeding the 300 mg daily dose. However, actually worldwide, the daily dose of 300 mg allopurinol is the dose used most frequently, and with these recent study data, the additional efficacy of the lesinurad 200 mg must be appreciated.

In the EMA SmPC, allopurinol should be prescribed at least 300 mg/day or 200 mg/day in patients with CKD, or febuxostat (dosing is not mentioned).

Statements

Precautions for a safe prescription	Lesinurad 400 mg QD monotherapy should be discouraged because of an increased renal toxicity risk [8]
Level 1b	
Efficacy	Lesinurad 200 mg QD added on allopurinol 300 mg daily or febuxostat 80 mg daily is effective to help getting more patients to the 0.30 mM serum target
Level 1b	Febuxostat/lesinurad 57% versus 41% febuxostat monotherapy [9]
Level 1b	More frequent with allopurinol/lesinurad than with allopurinol 300 mg daily: 3–7× more frequent with combined therapy than with monotherapy XOi [10, 11]

EULAR guideline

A task force from EULAR has published already 2 years ago an updated (pharmaco)therapeutic guideline on gout [2].

Pivotal herein are three overarching principles:

1. Patient education aiming at patient empowerment with emphasis on pathogenesis and comorbidities and the understanding of an individual serum urate target and principles of treating the attack as well as lifelong urate-lowering therapy in order to keep serum urate below this serum urate target
2. Advice regarding dietary abundance and lifestyle
3. The role of screening for associated comorbidities and cardiovascular risk

Furthermore, specific recommendations were formulated, and with the new uricosuric lesinurad, we need to draw attention to point 6, 8, and 9.

The serum target for complex gout patients (arthropathy with tophi, frequent attacks), mostly treated by rheumatologists, is set at 0.30 mM (5 mg/dL) because of beneficial effects on a group level shown at this serum urate target. In uncomplicated gout, a serum urate target of 0.36 mM may be quite adequate, and these patients will predominantly be treated by general practitioners (GPs).

When individually, serum urate targets cannot be reached with the optimal tolerated allopurinol dose, a switch to febuxostat should be considered. If serum urate target could not be reached with a XOi-monotherapy, the combination with a uricosuric should be considered. Up to now, from a practical point of view, a combination with benzbromarone or probenecid (if locally available) still was an option, but to date, there are no published data from larger randomized controlled trials on such combination therapies, which means that this combined treatment thus is considered "off-label." With regard to recent published data, the combination with the uricosuric lesinurad 200 mg has been shown to be an effective dose and safe option. If neither allopurinol nor febuxostat are tolerated by an individual, a last option would be the monotherapy with benzbromarone or probenecid, if locally available. In this case, the uricosuric option has an important prerequisite: Renal function has to be adequate (eGFR > 20 mL/min) and should be adequately monitored as well as fluid intake (> 2 L/day) should be sufficient (e.g., contraindicated in patients with higher degree of heart insufficiency).

Statements

Therapeutic indication	If the xanthine oxidase inhibition was optimized (including uptitration) and is not effective in reaching predefined serum urate target, a uricosuric, as an add-on, should be considered:
- Benzbromarone: according to SmPC, text should be administered as monotherapy; and as an add-on to XOi, it has to be considered off-label	Level 5
-Lesinurad: 200 mg plus an XOi	Level 1B
Therapeutic indication	Once an adequate dose of allopurinol, i.e., XOi cannot be continued/prescribed due to allergy, one may consider:
-Febuxostat monotherapy	Level 5
-Benzbromaron monotherapy	Level 5
-Febuxostat/lesinurad combination therapy	Level 1B

Specific setting regarding benzbromarone

Many European rheumatologists particularly from Spain, The Netherlands, and Germany (personal communication, some published small case series) became familiar with the use of the uricosuric benzbromarone and prescribed this uricosuric in about 5% of gout patients. Benzbromarone so far was the only alternative option available since the 1970th for gout patients who do not tolerate or are refractory to the XOi allopurinol. In 2003, this indication was limited and benzbromarone was taken off the market because of serious

adverse events reflecting liver dysfunction: The incidence at contracting a severe hepatotoxicity was estimated at 1:17,000. Because of the significance of the patient group fully dependent on this drug benzbromarone without any alternative regimen, it was again admitted to the Spanish and Dutch market, but only with the restriction that the gout patient could not tolerate allopurinol. In the SmPC text, a close monitoring was advised for liver enzymes during every 2-week period for the first year OR at regular time interval during the first 6 months OR as recommended by local or national recommendation. But also afterwards, one may need to consider potential idiosyncratic liver toxicity which can occur early or later during follow-up.

It is advised in general to monitor every 3 months for the transpeptidases ALT/AST and/or the cholestatic parameters AF/GGT plus total bilirubin.

In October 2014, the Medicines Evaluation Board granted the Pharmaceutical Company Prostrakan for a market access of benzbromarone 100 mg QD. Explicitly, one has described the indication: adult gout patients with an allopurinol-hypersensitivity, which is a clear cut contra-indication; or gout patients with other allopurinol intolerance of the effective dose. It has been taken into account that in Dutch trials, failures on allopurinol showed a higher responder rate on benzbromarone than on probenecid: 92% versus 65% [16, 17].

In 2014, the SmPC text has been reformulated. Our current advice therefore is:

Therapeutic Indication *Level 5*	Benzbromarone is an option in pharmacotherapy of crystal-proven gout and allopurinol[a]/febuxostat-- contra-indication (allergy/intolerance/ insufficient effect) if GFR > 20 mL/min: start the lowest dose available and consider uptitration The SmPC text restricts benzbromarone to be used only in gout patients with an allopurinol allergy or contra-indication. This is a leading rule once lesinurad is marketed, as there is proven efficacy and safety for lesinurad 200 mg QD in combination therapy with both XOi
Precautions for safety *Level 5*	Prior to starting benzbromarone, biochemical checks have to be performed regarding liver enzymes (at least the ALT) and renal function (at least glomerular filtration rate which should be exceeding 20 mL/min but preferably > 30 mL/min; and if possible, a fractional excretion rate of uric acid: FeUA) During the use of benzbromarone, a close clinical and laboratory monitoring is needed (e.g., development of diarrhea, liver enzymes, renal function) 1 month after start and every 6 months thereafter When diarrhea develops, the benzbromarone dose should be reduced (50 mg daily or 100 mg on alternate days) or stopped Caveat: simultaneous use of CYP2C9 metabolized drugs such as warfarin

[a]Individually up-titrated depending on tolerance/ renal function

Formulation of generic statement on appropriate use of lesinurad

Based on aforementioned arguments, the authors make a plea for the following:

A In crystal-proven gout patients, tophaceous or not, lesinurad 200 mg daily should be considered as an add-on with simultaneous XOi in cases where predefined serum urate target cannot be met with ongoing monotherapy XOi
Level 1b (9,10,11)

B1 In cases with an allergy for both allopurinol and febuxostat, one has to consider to start a uricosuric versus no therapy at all
Based on the SmPC texts, benzbromarone monotherapy then is to be preferred
Level 1b (8,18,19)

B2 Lesinurad 200 mg daily can be considered in cases with inefficacy/intolerance to benzbromarone, but always in combination therapy with either allopurinol/febuxostat
Level 1b (9,10,11)

C When a uricosuric monotherapy is used a prior and during follow-up, close clinical and laboratory monitoring should be done for (prior, after 1 month, and then at least every 6–12 months)
- Renal function (serum creatinine/GFR)
- Liver function tests particularly when benzbromarone is used according to national guidelines
Level 5

Conclusion

Since decades, the therapeutic options to lower serum uric acid levels were restricted to only a few agents. Even studies with the novel febuxostat showed that around 40–30% of gout patients still do not reach the defined target serum urate levels < 6 mg/dL (0.36 mM/L), much less the more stringent < 5 mg/dL (0.30 mM/L). Recently, a phase 3 study program of the new uricosuric lesinurad was completed successfully. With regard to the available data, the authorities FDA and EMA approved lesinurad as an add-on option in combination to any of the two xanthine oxidase inhibitors (XOi) if the treatment with XOi monotherapy is not adequate, i.e., sufficient in reaching the serum urate level recommended by different medical societies. This additional uricosuric treatment option will help us to further improve the management of our gout patients once appropriately used.

Compliance with ethical standards

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