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PERSPECTIVE

What is the Place for Uricosuric Agents in Gout Management?

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The auto-inflammatory rheumatic disorder gout is a worldwide problem [1]. It causes pain and loss of function when inadequately treated, leading to high costs and loss of productivity, income, and quality of life [1]. Gout is characterized by hyperuricemia and arousal of the NLRP3 *(nucleotide-binding domain, leucine-rich repeat-containing proteins)* inflammasome resulting in inflammatory arthritis and soft tissue rheumatism due to deposition of monosodium urate (MSU) crystals in joints and soft tissues around [2]. The clinical presentation of gout can be misleading, and other diseases can present in similar ways. In the elderly, gout is often not diagnosed as it frequently presents in the hands of elderly slim women and men [3]. The article focuses the gout management with particular attention to the uricosuric agents. Discussing anti-inflammatory medications details is our study limitation.

1. HOW TO TREAT THE GOUTY PATIENT?

Gout management includes non-pharmacological and non-pharmacological interventions [4-7]. Advanced age, renal dysfunction, potential drug interaction, and self-medications, especially in developing countries, could make gout treatment difficult with increased morbidity, disability, and mortalities [4, 5]. Lifestyle management such as preventing obesity, limiting alcohol, avoiding seafood, and fructose-containing drinks are essential non-medicinal strategies [5-7]. However, NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) are the mainstay of acute gouty attacks [4, 6-9]. When attacks are more frequent (three times yearly), strategies are to be taken for achieving serum uric acid (sUA) levels below the MSU saturation point, resulting in the long-term disappearance of signs and symptoms of gout [9]. Xanthine oxidase inhibitors (XOIs) (allopurinol, and febuxostat) and uricosuric agents (benzbromarone, sulfinpyrazone, and probenecid) are the two classes of urate-lowering therapies(ULTs) used in the disorder over the years [6-8]. Current *European League Against Rheumatism* (EULAR) management guidelines recommend the maintenance of sUA to <6.0 mg/dL (<357 mmol/L) in gouty patients, as treated by general practitioners, and even <5.0 mg/dl in patients with severe gout (gout with tophi, chronic arthropathy, frequent attacks) through a combination of lifestyle management and pharmacotherapy [7, 8]. *American College of Rheumatology* (ACR) sets the sUA target at<6 mg/dl [9]. However, many clinicians wonder what the place is of the uricosuric drug in the treatment of gout. For that reason, we decided to summarize the newest insights. Table **1** [18-22, 25-30] enlists research on new uricosuric agents [18-30].

2. PHARMACOTHERAPY

NSAIDs (selective and non-selective), steroids (oral, intra-articular, and intramuscular), neutrophil chemotaxis inhibitors (colchicine), and ULTs (XOIs and uricosuric agents) are used in gout to relieve symptoms, lower sUA, and dissolve tophus [6-9]. Pharmacotherapy in gout should also involve stopping diuretics as the first-line option for hypertension (HTN), if possible, and replacing these with no serum UA increasing medications, for example, losartan potassium and calcium channel blockers [6, 7]. Avoidance of low-dose aspirin, angiotensin receptor blockers (ARBs) other than losartan potassium [9], and adding lipid-lowering agents (statins and or fenofibrate) also help in maintaining target sUA and are conditionally recommended by ACR [7, 9].

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Table 1. Clinical studies on new uricosuric agents in hyperuricemia and gout management.

Study	Drugs	Comparators	Setting	Outcome Measures	AEs and SAEs
CLEAR1 (2017) (RCT) [18]	Lesinurad 200 and 400 mg added to allopurinol	Allopurinol monotherapy	Gout with moderate renal impairment	Lesinurad 200 / 400 mg - allopurinol therapy significantly achieved target sUA by 6-month over allopurinol monotherapy; no superiority of combination regimes over allopurinol monotherapy to reduce gout flares and tophi resolution.	AEs reported with allopurinol, allopurinol - lesinurad (200), and allopurinol-lesinurad (400) and were 68.7 %, 73.1 %, and 77.6 %, respectively; SAEs were 5.5 %, 4.5 %, and 8.0 %, respectively.
CLEAR2 (2017) (RCT) [19]	Lesinurad 200/400 mg added to allopurinol	Allopurinol monotherapy (≥300 mg/day, ≥200 mg/day)	Gout with moderate renal impairment	Target sUA achieved more with combination ULT over lesinurad and allopurinol monotherapy.	AEs reported with allopurinol, allopurinol-lesinurad (200), and, allopurinol-lesinurad (400) were 70.9 %, 74.5 % and 80.5 % respectively; SAEs were reported in 3.9 %, 4.4 % and 9.5 % of patients, respectively; higher renal AEs (raised serum creatinine, blood urea, and renal failure) were with increased lesinurad.
Dalbeth *et al*. (2017) (RCT) [20]	Lesinurad 400 mg, 200 mg to add febuxostat 80 mg	febuxostat 80 mg monotherapy	Tophaceous gout	sUA achieved at 6-month 6 with lesinurad 400 mg-febuxostat, but not with lesinurad 200-febuxostat 80 mg compared with febuxostat alone. Lesinurad 200 / 400 mg plus febuxostat significantly reduced tophi size.	AEs were 72.5 %, 82.1 %, and 82.6 % in the febuxostat group, febuxostat-lesinurad (200), and febuxostat-lesinurad (400), respectively. SAEs were reported higher with increased lesinurad. Renal AEs was higher with higher lesinurad groups (8.5 % vs. 10.1 %, with lesinurad 200 mg and lesinurad 400 mg, respectively).
Dalbeth *et al*. (2019) (RCT) [22]	lesinurad and febuxostat in the 12-month core CRYSTAL study continued at the same doses in the extension study for 2 years - febuxostat 80 mg were randomized to lesinurad 200 or 400 mg	ULT monotherapy.	Tophaceous gout	Progressive reduction of tophus size to at least complete resolution to one tophus, reduction of gout flares requiring treatment over the year 2.	AEs were higher with increased lesinurad doses in year-2: lesinurad 200 continued to 200 crossover (34 % to 45.2 %); lesinurad 400 continued to 400 crossover (34.3 % to 53.5 %); SAEs including renal-events were almost similar in both continued lesinurad dose groups.
Fitz-Patrick *et al*. (2019) (RCT) [25]	Verinurad 7.5, and 12.5 mg	Allopurinol 100 mg twice / day	Symptomatic hyperuricemia and gout	Verinurad monotherapy resulted in sustained reductions in sUA in asymptomatic hyperuricaemia and gout. Allopurinol 100 mg was statistically superior to verinurad 7.5 mg	AEs were similar in both groups. SAEs were 2.4 % in the placebo group and 11.6 % in the verinurad group
Stack *et al*. (2020) (RCT) [26]	Verinurad 9 mg plus febuxostat 80 mg	Placebo at 12 and 24 weeks	hyperuricemia, albuminuria, and T2DM.	Lower UACR in the verinurad plus febuxostat group than placebo at 12 and 24 weeks. Lower sUA among verinurad recipients. No clinically meaningful changes in eGFR and serum creatinine between verinurad and placebo. Verinurad plus febuxostat was well tolerated.	AEs - 63 % in verinurad and febuxostat-treated patients and 46 % in placebo-treated patients. SAEs were 16 % with verinurad plus febuxostat, 11 % with placebo. At week-24, Verinurad plus febuxostat had no apparent effect on eGFR over placebo.
Stack *et al*. (2021) (RCT) [27]	Oral once-daily verinurad 9 mg - febuxostat 80 mg - dapagliflozin 10 mg	Verinurad 9 mg -febuxostat 80 mg - placebo	Patients with asymptomatic hyperuricemia	Lower mean peak urinary UA excretion in both regimes; sUA were lower with the dapagliflozin regime.	Overall, 10/35 (29 %) subjects had AEs across both groups, with 16 events occurring in total. Most common AEs were gastrointestinal related (13.9 % of all patients). No significant elevations in creatinine were reported. No SAEs were reported.
Iqbal *et al*. (2021) (Meta-analysis) [28]	Dotinurad 1, 2, and 4 mg in hyperuricemia and gout	Benzbromarone, febuxostat	Patient with gout and asymptomatic hyperuricemia in DM, HTN,	Dotinurad significant improve sUA in hyperuricemic and gout and the effect is comparable to other ULTs.	AEs, 50.2 % with dotinurad 2 mg over 45.9 % in the control group. SAEs were not reported in the treatment and placebo groups

(Table 1) contd…

Study	Drugs	Comparators	Setting	Outcome Measures	AEs and SAEs
Toshinari *et al*. (2021) (pooled analysis of two RCT) [29]	Dotinurad 2 and 4 mg	Not mentioned	Effects of dotinurad in HTN patients with gout or asymptomatic hyperuricemia	dotinurad lowers sUA; the higher the dose, the higher the effect; over 80 % cases, dotinurad causes sUA level of ≤6.0 mg/dL in both analyses.	Dotinurad-related AEs and SAEs were not reported.
Hosoya *et al*. (2020) (RCT) [30]	Dotinurad 0.5, 1, 2, 4 mg	Placebo	Gout, tophous with DM, HTN, and metabolic syndrome	The percentage of patients achieving sUA (≤ 6.0 mg/d) increases with higher dotinurad doses and 100 % with 4 mg.	AEs was not associated with dose escalation. SAEs were observed in three patients: Colon cancer and hemorrhagic diverticulum intestinal hemorrhagic occurred in the dotinurad 1 mg group; prostate cancer occurred in the dotinurad 2 mg group.

Note: CLEAR, Combination Study of Lesinurad in Allopurinol Standard of Care Inadequate Responders; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HTN, hypertension; RCT, randomized controlled trial; AEs, adverse effects; SAEs, severe adverse effects; sUA, serum uric acid; UACR, urinary albumin-creatinine ratio; UA, uric acid.

3. INCREASING DOSAGE ALLOPURINOL

Fixed-dose 300 mg/day allopurinol is a common practice in gout management, reaching a normalization of sUA levels in approximately 40-60 % of the cases [10]. This percentage can increase to 75-80 % by increasing the allopurinol dose, depending on the tolerance [10]. At higher doses, allopurinol is well-tolerated in Caucasians [7, 10]. However, some patients could trigger life-threatening allopurinol hypersensitivity syndrome (AHS), including Stevens-Johnson syndrome and toxic epidermal necrolysis [11]. AHS is reportedly common in people with the HLA-B*58:01 allele, especially among Asians and blacks; renal impairment and concomitant diuretics may trigger AHS [11]. Allopurinol in suboptimal doses leads to a 29-50% reduction in tophi size, and a higher amount will result in accelerated tophus dissolution [6, 10].

4. COMBINING ALLOPURINOL AND FEBUXOSTAT WITH URICOSURIC AGENTS (PROBENECID, BENZBROMARONE, AND SULFINPYRAZONE)

We have known three uricosuric agents for several decades, namely, sulfinpyrazone, probenecid (ACR favorite), and the more potent benzbromarone (EULAR favorite) [12, 13]. Sulfinpyrazone has no clinical use, and benzbromarone is almost taken from the Europe market [12]. Uricosurics are considered second-line gout managing agents, although, in the 2012 guidelines, the ACR recommends probenecid as the 1st-line alternative (evidence B, nonrandomized controlled trial) to XOIs [6].

Both probenecid and benzbromarone can lower sUA in cases where XOIs appear insufficient, intolerant, or ineffective [13]. Earlier in 2007, an open study revealed that benzbromarone monotherapy was more effective than allopurinol (200-300 mg/day); however, the allopurinol-probenecid combination effectively attained target sUA levels that were comparable to benzbromarone monotherapy [14]. Combining low-dose allopurinol with a uricosuric preparation normalizes sUA levels in 65-92% of the cases [7]. Both EULAR and ACR suggest that the combination of the XOI-benzbromarone/probenecid regime could be applied in cases where any XOI monotherapy (allopurinol/febuxostat) fails to achieve target sUA levels. Still, these suggestions are based on nonrandomized controlled trials or expert opinion only [6]. To our knowledge, no randomized controlled trials (RCT) with the combination of febuxostat and benzbromarone, sulfinpyrazone, or probenecid have been done, which could be an area of future research in gout management.

5. NEW URICOSURIC AGENT: LESINURAD

Lesinurad, a urate transporter1 (URAT1) and organic anion transporters (OAT4) inhibitor, increases proximal renal tubule urate excretion [15]. RDEA806, the prodrug for lesinurad, is a nonnucleoside reverse transcriptase inhibitor in trials for HIV treatment that was found to have significant hypouricemic properties [15]. Lesinurad was approved in 2015 by the FDA to treat gout only in combination with febuxostat or allopurinol, especially when the latter one is proved inadequate or inappropriate, e.g., due to adverse effects (AEs) [16]. Monotherapy of lesinurad was associated with more serious AEs, mainly due to reduced renal function, and thus to be discouraged [17]. The combination with allopurinol was studied in the Combination Study of Lesinurad in Allopurinol Standard of Care Inadequate Responders (CLEAR1) (Saag USA) and (CLEAR2) trials (Bardin Europe) and the combination with febuxostat in the Dalbeth *et al*., 2017 study [18-20]. The combination results in a dual-action by lowering the sUA as well as reducing urate production. These studies revealed the superiority of lesinurad-febuxostat or lesinurad-allopurinol over febuxostat or allopurinol monotherapy at 6-month follow-up [18-20]. Still, in both CLEAR studies, lesinurad resulted in higher rates of (in most cases reversible) elevations in the serum creatinine level, particularly with lesinurad 400 mg. The combination of allopurinol 300 and lesinurad 200 mg reduced sUA <6.0 mg/dl in 55.4% cases at month 6; however, it was 66% with lesinurad 400- allopurinol 300 preparation [21]. Besides, febuxostat 80 mg - lesinurad 200 achieved target sUA of <5.0 mg/dl at 6-month in 56.6%, hardly different from febuxostat 80 mg only (46.8%) [20]. Lesinurad-allopurinol combination

was not superior regarding the dissolution of tophus compared to allopurinol 300 mg alone. The number of patients with complete resolution (CR) of tophus was not different between groups of patients treated with febuxostat 80 mg only or when combined with lesinurad, at 12-month follow-up [19-21]; however, progressive reduction of tophus size to at least complete resolution to one tophus, and reduction of gout flares require treatment for a second year, as measured in the Combination Treatment Study in Subjects with Tophaceous Gout with Lesinurad and Febuxostat (CRYSTAL) extension study [22]: 196 of 235 participated in the CRYSTAL study, enrolled in the extension study. Patients who received lesinurad plus febuxostat therapy continued to be at sUA target with a progressive increase in the at least one tophus CR, progressive reduction in tophus size, and decrease in gout flares required treatment in the second year [22]. AEs were consistent with those observed in the core study [22]. All these studies are biased as they compared lesinurad combinations with a drug that failed in the studied population. Apart from that, the analyses of Saag and Dalbeth contain a rather severe group of gouty patients [18, 20]. In patients treated with lesinurad 200 mg monotherapy, impaired kidney function can be observed, including kidney failure, but with an even greater frequency in the 400 mg group (Table **1**) [17]. For that reason, the US FDA only approved the 200 mg lesinurad dose in combination with allopurinol for patients' refractory to allopurinol [18]. Only the lower dose of lesinurad 200mg daily as an add-on therapy to XOI may have additional clinical value in selected cases and get the FDA's green light. Lesinurad was taken off the US and Europe market, respectively, in 2019 and 2020, though not because of AEs, only because of poor selling [23]. Later, In May 2021, in Ukraine, a Phase-III study of lesinurad in patients with hyperuricemia was discontinued [23].

6. NEWER URICOSURIC DRUGS IN THE PIPELINE

Verinurad is a new, highly potent, and specific URAT1 inhibitor that reduces sUA levels [24]. In a recent multicenter RCT, verinurad monotherapy resulted in sustained reductions in sUA in Japanese and US patients [25]. Dose-dependent responses of verinurad were observed in reducing sUA - as the dose increased, the more reduction of sUA happened. Verinurad 12.5, but not 10 mg, was statistically superior to allopurinol 100 mg twice daily, while allopurinol 100 mg was more effective than verinurad 7.5 mg [25]. The most frequently reported treatment-emergent AEs were upper respiratory infection and nasopharyngitis; however, HTN, arthralgia, headache, back pain, diarrhea, bronchitis, constipation, and increased serum creatinine were reported among verinurad-recipients over controls [25]. Serious AEs such as colitis, wound infection, dyspnea, postprocedural hemorrhage, subarachnoid hemorrhage, facial nerve palsy, and transient ischemic attack were more in the verinurad group than placebo [25]. Verinurad discontinuation was reported due to sinus tachycardia, increased blood pressure, nausea, hot flashes, hyperbilirubinemia, increased blood creatinine, acute renal failure, and prolonged QT in electrocardiogram plus sinus tachycardia. Some patients had spontaneously normalized serum creatinine, but in others only after discontinuation of verinurad (Table **1**) [25]. Further studies are needed.

In phase II multicenter RCT, verinurad (9 mg) plus febuxostat (80 mg) reduced sUA concentrations in type-2 diabetes mellitus (DM), albuminuria, and hyperuricemia patients [26]. However, its effect on renal function preservation requires a larger clinical trial [26]. Reduction of sUA level was notable with verinurad plus febuxostat over placebo at 12 and 24 weeks [26]; serum creatinine levels didn't significantly differ between the groups at 12 and 24 weeks [26].

The addition of anti-DM dapagliflozin (10 mg) *(sodium-glucose cotransporter-2 inhibitor)* to verinurad (9 mg) and febuxostat (80 mg) in an RCT with a wash-out period, led to a significant lowering of sUA, though without increasing urinary excretion of UA and adversely affecting renal function [27]. Dapagliflozin might reduce the production of UA, hence reducing the filtered load of UA in the kidney [27]. The most common AEs were gastrointestinal-related, occurring in 13.9% of all patients across both treatment periods. Gastrointestinal AEs were more in the placebo period than over the dapagliflozin period (8.3% over 5.7%. No significant elevations in creatinine were reported in this combination [27].

Dotinurad, another novel selective URAT1 inhibitor though without any inhibitory effect on organic anion transporter (OAT) 1 and 3 ABCG2 (responsible for renal and intestinal UA secretion) [28]. It brings significant improvement in sUA concentration in hyperuricemia with or without gout [28]. In a pooled analysis, dotinurad seen lowered sUA ≤6.0 mg/dL over 80% cases and hoped to be clinically helpful in managing hyperuricemia in HTN [28]. Dotinurad is highly effective at doses 1 mg, 2 mg, and 4 mg and well-tolerated at a dose of 2 mg [28]. At a daily maintenance dose of 2 or 4 mg, most hypertensive patients achieved the target sUA level of ≤6 mg/dL in a pooled analysis [29]. In the first RCT, Hosoya *et al*. described dotinurad as effective and safe in hyperuricemia and gout; however, they suggested further studies to compare those effects with benzbromarone or febuxostat [30].

Moreover, dotinurad's efficacy is not attenuated in mild to moderate renal impairment or hepatic impairment [29]. No findings raise safety concerns or specific liver injury [29]. However, more efficacy and safety trials regarding the long-term utility of dotinurad in treating hyperuricemia and gout should be done in phase IV studies [28]. The only systematic review related to the efficacy of dotinurad in patients with hyperuricemia with or without gout is based on four RCTs (study duration, 8 to 14 weeks) and revealed that the urate-lowering effect of dotinurad is comparable to that of febuxostat and benzbromarone [28].

7. URICOSURIC AGENTS IN CLINICAL PRACTICE

Probenecid is now the only uricosuric agent available in the US. Benzbromarone is used in some other countries [31]. Due to the high AEs profile, limited supply, and inefficacy in renal impairment, sulfinpyrazone is useless in clinical practice and has

not been focused in the current EULAR and ACR guidelines [7, 9, 32, 33]. Probenecid is well-absorbed orally with a dose-dependent half-life in plasma of 6-12 hours, which is prolonged by concomitant use of allopurinol [32]. Probenecid is metabolized in the liver, with <5% of the administered dose recovered in urine. A daily dose of 500-3000 mg is administered in two or three divided doses. Initiation may precipitate gout flares, and, as with all uricosuric agents, probenecid increases the risk of renal calculi. Up to 18% of patients develop gastrointestinal AEs, and 5% develop hypersensitivity and rash. One-third of patients become intolerant to, hence discontinue, probenecid. Benzbromarone is more potent than probenecid and sulfinpyrazone and is well-tolerated [32]. Benzbromarone is effective after renal transplant and can be used with a creatinine clearance (CCr) as low as 25 ml/min. When CCr drops below 20ml / min, benzbromarone will have no uricosuric effect anymore [32]. However, hepatotoxicity has led to its removal from some markets worldwide, and the actual risk remains controversial [32].

Before prescribing uricosuric agents, the following important points are to be considered: failure/contraindication of XOI, history of prior nephrolithiasis, and current renal function status (CCr >60 ml/min) [6, 7, 22]. A CCr level <45 ml/min does not allow the use of lesinurad, and regular monitoring of the kidney function is warranted, especially in cases where CCr < 60 ml/min [21]. The ACR did not strongly recommend uricosurics in gout management [9]. It says no to uricosuric agents in patients with renal calculi and moderate-to-severe chronic kidney disease (CKD) (stage >3) [9]. ACR voting panels conditionally recommend uricosuric agents as an add-on therapy to partially responsive XOI [9].

Currently, lesinurad is not available in Europe and not in the USA. Verinurad and dotinurad are not available yet, but experimental drugs are only. Lesinurad (plain and combination with XOIs) was expensive [34], and physicians have long time experience with XOIs and well-known uricosuric agents [35]. For these reasons, the pharmaceutical company decided to withdraw all lesinurad preparations from the market; there were no issues related to clinical efficacy or AEs [23, 34, 35]. Rheumatologists consider it a loss for allergic patients to allopurinol or who can not tolerate a higher dose of allopurinol. Allopurinol/febuxostat-probenecid or allopurinol/febuxostat-benzbromarone are probably a better alternative to the allopurinol/febuxostat-lesinurad combination. However, in a multicenter study, all-cause mortality and cardiovascular (CV) mortality were reported higher in long-standing febuxostat users than in allopurinol [36]. The same outcome was also documented in a meta-analysis [37]. Physicians should be aware of the long-term CV consequences of febuxostat.

To our knowledge, no RCT with the combination of febuxostat with probenecid or benzbromarone has been done. Adding benzbromarone100 mg to allopurinol is not prospectively studied, and thus off-label, the lower dose benzbromarone (10-50 mg/day) is available in Europe and Asian countries, but not in the USA [38]. Further investigations should be performed studying the combination of XOIs (allopurinol/febuxostat) with well-known uricosuric agents. Research on the combined preparation of XOIs and uricosuric-like agents, such as statins, fenofibrate, or losartan, could also yield positive outcomes [6, 9]. Verinurad and dotinurad are yet to appear in clinical practice. Like lesinurad, their price-benefit issue could also be essential to see how they survive treating hyperuricemia and gout in the coming days.

CONCLUSION

Gout patients in whom serum uric acid values are insufficiently controlled with low dosage allopurinol generally benefit from allopurinol dosage up-titration. If the target serum uric acid values are not reached, one may consider febuxostat. Adding a uricosuric could be a practical option if xanthine oxidase inhibitor is well-tolerated but not adequate in monotherapy settings. Head-to-head studies of uricosurics in an add-on setting are needed.

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CONFLICT OF INTEREST

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