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Review

Efficacy and safety of urate-lowering therapy in people with kidney impairment: a GCAN-initiated literature review

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Abstract

Objectives. The aim was to evaluate the efficacy, defined as achieving target serum urate <6.0 mg/dl, and safety of urate-lowering therapies (ULTs) for people with gout and chronic kidney disease (CKD) stages 3–5.

Methods. PubMed, The Cochrane Library and EMBASE were searched from 1 January 1959 to 31 January 2018 for studies that enrolled people with gout, who had an estimated glomerular filtration rate (eGFR) or creatinine clearance (CrCl) of <60 ml/min and exposure to allopurinol, febuxostat, probenecid, benzbromarone, lesinurad or pegloticase. All study designs other than case reports were included, except for people on dialysis, for whom we did include case reports.

Results. There were 36 reports with an analysis of efficacy and/or safety based upon renal function: allopurinol ($n = 12$), febuxostat ($n = 10$), probenecid ($n = 3$), benzbromarone ($n = 5$), lesinurad ($n = 5$) and pegloticase ($n = 1$). There were 108 reports that involved people with gout and renal impairment but did not contain any analysis on efficacy and/or safety based upon renal function: allopurinol ($n = 84$), febuxostat ($n = 14$), benzbromarone ($n = 1$), lesinurad ($n = 3$) and pegloticase ($n = 6$). Most studies excluded people with more severe degrees of renal impairment (eGFR or CrCl of <30 ml/min). For allopurinol, in particular, there was significant variability in the dose of drug used and the efficacy in terms of urate lowering, across all levels of renal impairment.

Conclusion. There is a lack of evidence regarding the efficacy and/or safety of currently used ULTs according to different levels of renal function. Future studies should include patients with CKD and should report study outcomes stratified by renal function.

Key words: gout, renal insufficiency, chronic, chronic kidney disease, gout suppressants, urate-lowering therapy

REVIEW

Key messages

- Conclusions about efficacy and safety of available urate-lowering therapies cannot be made.
- Future studies should include people with chronic kidney disease and report results by renal function whenever possible.

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Introduction

Gout is common in patients with chronic kidney disease (CKD). A systematic review and meta-analysis of epidemiological studies of adults with gout found that 24% had CKD stage 3 or greater (95% CI: 19, 28%) [1]. The prevalence of gout also increases as renal function declines, as demonstrated by a study of an age-standardized prevalence of gout of 2.9% among adults with an estimated glomerular filtration rate (eGFR) $\geq$90 ml/min and 24% among those with eGFR $<$60 ml/min [2]. This reciprocal increase is explained by the fact that two-thirds of urate excretion occurs through the kidneys and by the detrimental effects of hyperuricaemia on the kidneys, from stimulation of oxidative stress and activation of the renin–angiotensin system to interstitial inflammation and fibrosis [3].

Clinicians managing gout need to be mindful of how therapies for gout might influence or be influenced by kidney function. For instance, oxypurinol (the active metabolite of allopurinol) is excreted by the kidneys, resulting in higher plasma oxypurinol concentrations as kidney function declines. Uricosuric drugs also depend on renal filtration to provide their effect through the blockage of ion transporters in the renal tubules; therefore, they lose efficacy in advanced kidney disease. Treatment of gout is frequently suboptimal, and this is particularly so in people with concomitant CKD, primarily owing to concerns over adverse effects and efficacy of medications used in the management of gout [4]. For example, it is common practice to limit the allopurinol dose based on creatinine clearance (CrCl), although this approach results in $<$50% of patients reaching the serum urate (SU) target. Such adherence to renal-based dosing has never been proved to reduce the risk of severe adverse reactions to allopurinol, and there is increasing evidence that allopurinol can be increased safely beyond 'renal-based doses' in patients with CKD [5, 6]. Similar uncertainties exist for most urate-lowering therapies (ULTs) in gout.

The aim of this paper is to review the current literature on the safety and efficacy of ULTs used in the management of gout in people with CKD stages 3–5, in order to prioritize key areas for research in the management of gout in this high-need patient population.

Methods

Search strategy

PubMed, The Cochrane Library and EMBASE were searched from 1 January 1959 to 27 June 2017 and with a second search from 28 June 2017 to 31 January 2018 to capture any additional papers published during the main review phase. ULTs included were those currently approved for use in gout, including allopurinol, febuxostat, probenecid, benzbromarone, lesinurad and pegloticase. The specific search terms are detailed in Supplementary Table S1, available at *Rheumatology Advances in Practice* online. Literature searches on terms linking gout and ULT and dialysis and CKD with ULT were performed separately and subsequently merged.

Study selection

Studies were included if they enrolled people with gout, with an eGFR or CrCl of $<$60 ml/min, and exposure to the ULT of interest. All study designs other than case reports were included, with two exceptions: patients on dialysis, where case reports were considered, owing to the paucity of studies in these patients; and given that there are no randomized controlled trials (RCTs) of allopurinol hypersensitivity syndrome (AHS)/drug rash with eosinophilia and systemic symptoms, we included the large AHS studies, which also enrolled people without gout.

Studies were excluded from final abstraction if they were not available in English, primarily included people without gout (for example, asymptomatic hyperuricaemia), if information on CrCl/eGFR was not reported, if patients with gout and eGFR of $<$60 ml/min/1.73 m^2 were not enrolled, if they were letters, opinion articles or review articles, animal studies and basic science or purely laboratory-based studies.

Data extraction

Data were extracted from published reports and online supplementary material using an extraction form on an Excel spreadsheet. For assessing efficacy of the ULT of interest, the main outcome was the proportion of study participants who achieved the target SU level of $<$6.0 mg/dl stratified by renal function. When studies assessed more than one ULT, only the patients receiving the therapy of interest were analysed in the relevant sections of this review. Other data extracted were the study design, renal function exclusion criteria, the maximum dose of ULT allowed and dose given, and the number of participants according to renal function category. For safety, any reported adverse event data stratified by renal function were collected. Two authors independently assessed studies for inclusion and extracted data (L.K.S. and H.F. for allopurinol; A.L.G. and A.B.V.-S. for all other drugs). Discrepancies were resolved by discussion. Risk of bias was not assessed formally.

Data synthesis

Owing to methodological diversity, data are presented by structured tabulation with a qualitative summary.

Results

The flowcharts of study selection for allopurinol, febuxostat, probenecid, benzbromarone, lenisurad and pegloticase are shown in Supplementary Figs S1–S6, available at *Rheumatology Advances in Practice* online. There were 36 reports with an analysis of efficacy and/or safety based upon renal function: allopurinol (n = 12),

febuxostat ($n = 10$), probenecid ($n = 3$), benzbromarone ($n = 5$), lesinurad ($n = 5$) and pegloticase ($n = 1$). There were 108 reports that involved people with gout and eGFR <60 ml/min but did not contain any analysis on efficacy and/or safety based upon renal function: allopurinol ($n = 84$), febuxostat ($n = 14$), benzbromarone ($n = 1$), lesinurad ($n = 3$) and pegloticase ($n = 6$). For probenecid, six studies were excluded because they reported having evaluated subjects with renal dysfunction but used old methods to define renal function (decreased urea clearance, elevated non-protein nitrogen), making appropriate comparison across other studies impossible [7–12].

Allopurinol

Studies with analysis based on renal function

Table 1 summarizes the main characteristics of the 12 articles that reported the efficacy of allopurinol stratified by renal function. These articles reported data from 12 different studies. Six of these studies were RCTs. Seven of the 12 studies excluded participants with more severe degrees of renal dysfunction, most commonly those with eGFR of <30 ml/min. Seven studies specified a maximum allowable dose of allopurinol, and the dosing was variable between studies. These 12 studies included a total of 21 068 participants who had data for serum urate stratified by renal function. Most but not all studies reported renal function in such a way as to allow grouping of participants into categories of renal function.

The percentage of participants achieving target SU of <6.0 mg/dl varied depending on renal function: for participants with eGFR ≥60 ml/min, the values ranged between 23.3 and 75%, for eGFR of 30–<60 ml/min, the values ranged between 20.2 and 76.4%, and for eGFR <30 ml/min, the values ranged between 18.8 and 64.3% (Table 1). Only 4 of the 12 studies reported adverse events according to renal function. The rates of adverse events were not found to differ according to renal function (Table 2).

Studies without analysis based upon renal function

There were 84 articles reporting data from 83 different studies that included participants with varying degrees of renal impairment but did not have an analysis of efficacy and/or safety according to renal function. A summary of the characteristics of these studies is shown in Supplementary Table S2, available at *Rheumatology Advances in Practice* online.

Allopurinol hypersensitivity syndrome and chronic kidney disease

CKD has long been recognized as one risk factor for severe allopurinol-related adverse reactions [46]. In the largest case series of AHS to date, 182/376 (48.4%) had renal impairment [47]. However, AHS can occur in people with normal renal function, indicating that other factors must be involved. For example, concomitant diuretic administration has been associated with AHS [48, 49]. Allopurinol starting dose and the presence of HLA-B*5801 have more recently been identified as important risk factors for AHS. However, the interaction between the identified risk factors, particularly allopurinol starting dose, renal impairment and HLA-B*5801, appears to be important in increasing the risk (Table 3).

A key challenge is that most of the large cohorts of patients used to examine risk factors for AHS have included people with gout in addition to those treated for other conditions, including asymptomatic hyperuricaemia. It has been suggested that asymptomatic hyperuricaemia itself is associated with an increased risk of AHS [odds ratio (OR) 2.08 (95% CI: 1.94–2.24)] and an increased risk of death from AHS [OR 2.32 (95% CI: 1.79–3.01)] [52].

Febuxostat

Studies with analysis based on renal function

The main characteristics of the 10 studies that reported febuxostat efficacy based on renal function are summarized in Table 1. There were only three RCTs [13, 14, 30]. Although APEX (Allopurinol Placebo-Controlled Efficacy Study of Febuxostat) and CONFIRMS were already fully described in Table 1, the study by Chohan *et al.* [18] was included for adding partial data from the FACT (Febuxostat Versus Allopurinol Controlled Trial) stratified by renal function. There was one case report of a patient on dialysis [28]. The 10 studies included >2700 subjects with gout using febuxostat, with ≥920 of them having eGFR of <60 ml/min/1.73 m^2. Five additional studies included [57–61] reported supplementary analysis on data from studies already described.

The percentage of study participants achieving target SU of <6.0 mg/dl varied depending on the febuxostat dose, rather than renal function. Considering the 10 studies, only 1 RCT and 1 observational study presented safety analysis based on renal function. There was no obvious difference in adverse events according to renal function (Table 2).

Studies without analysis based upon renal function

A summary of the characteristics of the 14 studies identified that included participants with CKD but did not report efficacy and/or safety data based on renal function is shown in Supplementary Table S2, available at *Rheumatology Advances in Practice* online.

Probenecid

Studies with analysis based on renal function

The main characteristics of the three studies included are described in Table 1; all of them provided efficacy data based on renal function. Only one was an RCT [31], which compared the uricosuric effects of probenecid and zoxazolamine use over 3 days. Among the 10 participants who used probenecid at a dose of 1.5 g/day, one study participant had CKD, with a CrCl of 59.5 ml/min. Within the short study period, his SU fell from 10.7 to 7.9 mg/dl, which was a significant reduction, despite not reaching the SU target of <6 mg/dl.

TABLE 1 Studies reporting efficacy of urate-lowering therapies based on renal function

First author (year) (trial name)	Design	Renal function exclusion criteria eGFR/CrCl (ml/min) or creatinine (mg/dl)	Maximum ULT dose according to protocol (mg/day)	Actual or mean dose (mg/day)	Number of participants by eGFR/CrCl (ml/min) (% with SU of <6 mg/dl)[a]				Total *n*
					≥90	60–<90	30–<60	<30	
ALLOPURINOL									
Schumacher (2008) (APEX) [13]	RCT	Cr >2.0 mg/dl	Cr ≤1.5 mg/dl: 300 Cr 1.5–≤2 mg/dl: 100	300: *n* = 258 100: *n* = 10	Cr ≤1.5 mg/dl: *n* = 258 (23.3) Cr 1.5–≤2.0 mg/dl: *n* = 10 0				268 (22.4)
Becker (2010) (CONFIRMS) [14]	RCT	eCLcr <30	eCLcr l ≥ 60: 300 eCLcr <60: 200	300: *n* = 610 200: *n* = 145	255 (41.7)	365 (46.3)	136 (31.6)	0	755 (42.1)
Jennings (2014) (FAST) [15]	RCT (baseline data of first 400 participants)	eGFR <30	900	200 at baseline, 300 in 144 who were uptitrated[b]	332 (64.8)		68 (58.8)	0	400 (63.8)
Stamp (2017) [16]	RCT (*post hoc* analysis of refs 3 and 4 in Supplementary Table S2, available at *Rheumatology Advances in Practice* online)	None	900	CrCl >60: 460 CrCl 30–<60: 365 CrCl <30: 250	88 (75)		71 (76.4)	24 (64.3)	183
White (2018) (CARES) [17]	RCT	eCLcr < 30	eCLcr l ≥ 60: 600 eCLcr l < 60: 400	200 21.8%, 300 44.6%, 400 25.2%, 500 4.3%, 600 4.1%	228	1231	1631	0	3090 (75)
Chohan (2012) (FACT/APEX/CONFIRMS) [18][c]	*Post hoc* analysis of RCTs	As per refs [13, 14]. FACT: Cr >1.5 mg/dl or CrCl <50	300	100: *n* = 2, 200: *n* = 32, 300: *n* = 40	2 (50)	18 (50)	54 (44.4)	0	76 (74 analysed) (45.9)
Becker (2015) (LASSO) [19]	Open label	CrCl <30	Local guidelines	14.4%: <300 65.4%: 300 20.2%: >300	813 (32)	654 (39)	257 (41)	6	1732 (35.9)
Bowie (1967) [20]	Open label	Not specified	Not specified	342	*n* = 14. Mean CrCl 37 (66.7% based on average uric acid 1–6 months)				14 (66.7)
Doogue (2016) [21]	Observational	All HD	100	100	0	0	0	5 (HD)	5
Fuldeore (2011) [4]	Retrospective	Dialysis	Not specified	CKD0/1: 268.93 CKD2: 261.63 CKD3: 248.08 CKD4: 241.54	1855 (25.6)	826 (23.3)	312 (20.2)	129 (18.8)	3122
Hatoum (2014) [22][d]	Retrospective	Not specified	Not specified	184.9	1038 (29.1)	4437 (31.3)	5053 (30.6)	920 (28.1)	10 119 (29.2)
Hmar (2015) [23][e]	Audit of medical records	Not specified	Not specified	211 (range 25–600)	Not clear	465 (0.27)	322 (0.39)	126 (0.38)	1304
FEBUXOSTAT									
Schumacher (2008) (APEX) [13]	RCT	Cr >2.0 mg/dl	240	80 mg *n* = 267 120 mg *n* = 269 240 mg *n* = 134	Last 3 monthly SU <6.0 mg/dl Cr ≤1.5 mg/dl (*n* = 640): 80 mg (48.2) | 120 mg (65.9) | 240 mg (69.0) Cr 1.5–≤2.0 mg/dl (*n* = 25): 80 mg (44.4) | 120 mg (45.4) | 240 mg (60.0)				670
Becker (2010) (CONFIRMS) [14]	RCT	eCLcr <30	80	40 mg *n* = 757 80 mg *n* = 756	531 40 mg (37.4) 80 mg (58.1)	716 40 mg (52.1) 80 mg (71.7)	266 40 mg (43.1) 80 mg (71.3)	0	1513
Chohan (2011) [24]	Study without independent comparison group	Not specified	100	20 mg *n* = 3 40 mg *n* = 4 60 mg *n* = 1 80 mg *n* = 3 100 mg *n* = 1 Withdrawn *n* = 1	1 (100) 80 mg: 1/1	3 (66.6) 40 mg: 1/1 60 mg: 1/1 80 mg: 0/1	5 (66.6) 40 mg: 0/1 80 mg: 1/1 100 mg: 1/1 SU unknown for two patients: Fbx 0 mg and 40 mg	4 (100) 20 mg: 3/3 40 mg: 1/1	13

(continued)

Table 1 Continued

First author (year) (trial name)	Design	Renal function exclusion criteria eGFR/CrCl (ml/min) or creatinine (mg/dl)	Maximum ULT dose according to protocol (mg/day)	Actual or mean dose (mg/day)	Number of participants by eGFR/CrCl (ml/min) (% with SU of <6 mg/dl)[a]				Total *n*
					≥90	60–<90	30–<60	<30	
Chohan (2012) (FACT/APEX/CONFIRMS) [18]	*Post hoc* analysis of RCTs (female subjects included in three RCTs: FACT, APEX and CONFIRMS)	FACT: Cr >1.5 mg/dl or CrCl < 50 APEX: Cr >2.0 mg/dl CONFIRMS: CrCl <30	240	40 mg *n* = 35 80 mg *n* = 74 120 mg *n* = 21 240 mg *n* = 7	10 (90.0) • 40 mg: 1/2 • 80 mg: 7/7 • 120 mg: 1/1 • 240 mg: 0/0	43 (83.7) • 40 mg: 8/10 • 80 mg: 21/25 • 120 mg: 4/5 • 240 mg: 3/3	84 (72.6) • 40 mg: 10/23 • 80 mg: 35/42 • 120 mg: 12/15 • 240 mg: 4/4		137
Son (2015) [25]	Study without independent comparison group	Not specified	Not specified	Not specified	0	0	13 (CrCl <45) SU (mg/dl) • baseline: 8.8 ± 1.9 • 6 months: 5.6 ± 2.1	12 (6 on dialysis) SU (mg/dl): CKD4 • baseline: 8.9 ± 2.8 • 6 months: 6.7 ± 4.4 CKD5: • baseline: 7.2 ± 0.7 • 6 months: 4.9 ± 2.2	25
Quilis (2015) [26]	Study without independent comparison group	Not specified	80	Not specified	41 (77.5)			14 (83.3)	55
Lim (2016) [27]	Study without independent comparison group	Not specified	160	Not specified	0	0	0	294 HD: *n* = 32 PD: *n* = 17 Mean SU (mg/dl): • baseline 9.61 ± 2.18 • 3 months 4.97 ± 1.84 • 12 months 4.98 ± 2.33	294 (224 with gout)
Frassetto (2016) [28]	Case report	N/A	80	80	0	0	0	1 HD (100) SU (mg/dl): • Baseline: 10.8 • Increased HD: 5.4 • Increased HD+Fbx80 mg: <1.5	1
Juge (2017) [29]	Study without independent comparison group	CrCl >30	120	40–120	0	0	0	CKD4 *n* = 60 CKD5 *n* = 13 (67.1)	73
Gunawardhana (2018) [30]	RCT, multicentre, placebo-controlled, double-blind	eGFR <30 or ≥60	80	40 mg IR *n* = 37 40 mg XR *n* = 39 80 mg IR *n* = 37 80 mg XR *n* = 38	0	0	189 40 mg IR (32.4) 40 mg XR (53.8) 80 mg IR (59.5) 80 mg XR (55.3)	0	189
PROBENECID									
Rivera (1961) [31]	RCT (probenecid *vs* zoxazolamine for 3 days)	None	1500	1500	6 (83)	3 (100)	1 0	0	7
Stocker (2011) [32]	Study without independent comparison group	None	2000	250–2000	5 patients with CrCl <50: 80% achieved SU <5 mg/dl 15 patients with CrCl ≥50: 100% achieved SU <5 mg/dl				20
Pui (2013) [33]		None	Not specified	Mean: 1150	42 patients with eGFR >50 (36) 11 patients with eGFR 30–50 (45)			4 0	57

(continued)

Table 1 Continued

First author (year) (trial name)	Design	Renal function exclusion criteria eGFR/CrCl (ml/min) or creatinine (mg/dl)	Maximum ULT dose according to protocol (mg/day)	Actual or mean dose (mg/day)	Number of participants by eGFR/CrCl (ml/min) (% with SU of <6 mg/dl)[a]				Total *n*
					≥90	60–<90	30–<60	<30	
	Study without independent comparison group								
BENZBROMARONE									
Perez-Ruiz (1999) [34]	RCT	CrCl <20 or >80	200	103 ± 23 (100–150)	17 (94.1) CrCl: 54.5 ± 17.5 – benzbromarone users at the lowest range of CrCl had higher baseline SU and needed higher doses of benzbromarone				17
Kumar (2005) [35]	Study without independent comparison group	None	100	100	0	1 (33.3)	4	1	6
Fujimori (2011) [36]	Study without independent comparison group	Normal kidney function or CKD stages 1–2	200	12.5–200	0	0	32 eGFR 46.2 ± 11.5 SU (mg/dl) • Baseline 8.5 ± 0.9 • After benzbromarone 6.1 ± 0.8	3: 2 CKD4 (≥50) 1 CKD5 0	35 (31 had gout)
Oh (2011) [37]	Study without independent comparison group	eGFR ≥60 or <15	100	47.5 ± 29.1 (25–100)	0	0	Baseline eGFR 38.4 ± 8.3 (70)		20
Stamp (2016) [38]	Survey	None	200	25–200 (median = 100)	35 eGFR 50.3 ± 22.8 (62.6) There was no statistically significant difference in the number of patients who achieved SU <6.0 mg/dl based on eGFR. However, at each eGFR, numerically, more people on benzbromarone achieved SU <6.0 mg/dl compared with Allo and probenecid		55	22	117
LESINURAD									
Hagerty (2011) [39]	Two phase 2b studies	Severe renal impairment	600	200–600 mg	Median SU reduction with the 400 mg dose: • Monotherapy: Normal renal function: 32% Mild to moderate renal impairment: 28% • Combination with Allo: Normal renal function: 21% Mild to moderate renal impairment: 25%			0	331
Dalbeth (2015) (CRYSTAL) [40]	RCT	CrCl <30	400	200 mg *n* = 103 400 mg *n* = 106	76 Fbx+Lesu200 (73) Fbx+Lesu400 (76.9)	83 Fbx+Lesu200 (65.8) Fbx+Lesu400(73.3)	50 Fbx+Lesu200 (64.3) Fbx+Lesu400 (59.1)	0	209
Saag (2015) (CLEAR 1/CLEAR 2) [41]	Combined analyses from two RCTs	CrCl <30	400	200 mg *n* = 394 400 mg *n* = 395	318 Allo+Lesu200 (59.7) Allo+Lesu400 (62.9)	328 Allo+Lesu200 (61.5) Allo+Lesu400 (67.1)	143 Allo+Lesu200 (52.7) Allo+Lesu400 (53.6)	0	789
Saag (2017) (CLEAR 1) [42]	RCT	CrCl <30	400	200 mg *n* = 200 400 mg *n* = 200	159 Allo+Lesu200: 83 Allo+Lesu400: 76	155 Allo+Lesu200: 72 Allo+Lesu400: 83 At month 6: • Allo+Lesu200 20% > Allo • Allo+Lesu400 24% > Allo	86 Allo+Lesu200: 45 Allo+Lesu400: 41 At month 6: • Allo+Lesu200 16% > Allo • Allo+Lesu400 21% > Allo	0	400

(continued)

Table 1 Continued

First author (year) (trial name)	Design	Renal function exclusion criteria eGFR/CrCl (ml/min) or creatinine (mg/dl)	Maximum ULT dose according to protocol (mg/day)	Actual or mean dose (mg/day)	Number of participants by eGFR/CrCl (ml/min) (% with SU of <6 mg/dl)[a]				Total *n*
					≥90	60–<90	30–<60	<30	
Bardin (2017) (CLEAR 2) [43]	RCT	CrCl <30	400	200 mg *n* = 204 400 mg *n* = 199	165 Allo+Lesu200: 80 Allo+Lesu400: 85	180 Allo+Lesu200: 95 Allo+Lesu400: 85 At month 6: • Allo+Lesu200 33% > Allo • Allo+Lesu400 42% > Allo	58 • Allo+Lesu200: 29 • Allo+Lesu400: 29 At month 6: • Allo+Lesu200 34% > Allo • Allo+Lesu400 41% > Allo	0	403
PEGLOTICASE									
Yood (2014) [GOUT1 (C0405) and GOUT2 (C0406)] [44]	*Post hoc* subgroup analysis of two RCTs (phase 3) and their open-label extension study	Renal dialysis	8 mg q2wk	Patients with CKD3 or 4: • 8 mg q2wk *n* = 42 • 8 mg q4wk *n* = 41 • Placebo *n* = 20	34 (32)	74 (23)	80 (35)	23 (39)	211

Allo: allopurinol; APEX: Allopurinol Placebo-Controlled Efficacy Study of Febuxostat; CARES: Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities trial; CKD: chronic kidney disease; CLEAR: Combining Lesinurad with Allopurinol Standard of Care in Inadequate Responders; CONFIRMS: Urate-Lowering Efficacy and Safety of Febuxostat in the Treatment of the Hyperuricaemia of Gout; Cr: creatinine; CrCl: creatinine clearance; eCLcr: estimated creatinine clearance; CRYSTAL: Combination Treatment Study in Subjects with Subcutaneous Tophaceous Gout with Lesinurad and Febuxostat; eGFR: glomerular filtration rate; ESRD: end-stage renal disease; FACT: Febuxostat Versus Allopurinol Controlled Trial; FAST: Febuxostat versus Allopurinol Streamlined Trial; Fbx: febuxostat; HD: haemodialysis; IR: immediate release; LASSO: Long-term Allopurinol Safety Study Evaluating Outcomes in Gout Patients; Lesu: lesinurad; N/A: not applicable; PD: peritoneal dialysis; q2wk, every 2 weeks; q4wk, every 4 weeks; RCT: randomized controlled trial; SU: serum urate; ULT: urate-lowering therapy; XR: extended release. [a]When available. [b]Median. [c]Included because it contained data from the FACT study [45] stratified by renal function that was not reported in the original paper. [d]17 199 people were prescribed allopurinol initially. Numbers of subjects included per renal function category are according to 11 488 that had baseline renal function reported. 10 119 had at least one serum urate and were analysed for achieving serum urate goal within 6 months. Numbers in brackets indicate the percentage achieving serum urate goal within 6 months, according to renal function category. [e]Numbers in brackets for this paper correspond to mean urate concentration (in millimoles per litre).

TABLE 2 Adverse events, stratified by renal function, in studies that report efficacy according to renal function[a]

First author (year) (trial name)	Notable findings
ALLOPURINOL maintenance dose	
Becker (2010) (CONFIRMS) [14]	Overall, 57.3% of subjects taking allopurinol experienced at least AE. The AE rate in subjects with mild or moderate renal impairment was 289/501 (57.7%). Overall, 7% of patients taking allopurinol developed a rash and one subject experienced a severe desquamating eruption. Overall serious AE rate 4.1% for all allopurinol users.
Stamp (2017) [16]	Seventeen deaths occurred during study period: 4/88 CrCl > 60, 7/71 CrCl 30–<60, 6/24 CrCl <30. The type and number of SAEs were as expected and were similar between groups[b].
White (2018) (CARES) [17]	Primary endpoint (composite endpoint of cardiovascular death, non-fatal MI, non-fatal stroke, urgent revascularization) and cardiovascular mortality by renal function group, for subjects taking allopurinol: eCLcr ≥90/60–89/30–59: 7.5%/7.5%/13% and 1.3%/1.5%/4.8%.
Becker (2015) (LASSO) [19]	TEAEs occurred at similar instances in categories divided by baseline renal function[c]. Overall rate of TEAE possibly related to allopurinol 10.7%. Most common TEAEs possibly related to allopurinol, occurring in patients on <300, 300 and >300 mg categories were alanine aminotransferase increase (2.0, 1.1 and 2.0%), diarrhoea (1.2, 1.1 and 2.0%) and rash (2.0, 0.8 and 0.3%). Serious AEs occurred in 2.9%, none considered to be related to allopurinol.
FEBUXOSTAT	
Becker (2010) (CONFIRMS) [14]	Overall, 56.7 and 54.2% of subjects taking febuxostat 40 and 80 mg, respectively, experienced at least one AE. The AE rate in subjects with mild or moderate renal impairment was 56% (268/479) among subjects taking febuxostat 40 mg and 54% (270/503) among those taking febuxostat 80 mg. Overall serious AE rate was 2.5 and 3.7% for febuxostat 40 and 80 mg, respectively. The most frequently reported AEs in subjects with renal impairment were the same as those reported for all subjects. Rates of diarrhoea were higher among subjects with moderate renal impairment receiving febuxostat (8–10%), compared with subjects with moderate renal impairment receiving allopurinol (7%).
Quilis (2015) [26]	Febuxostat was discontinued in 11 (20%) patients (in 3 cases owing to skin reactions), but it did not differ regarding eGFR subgroups.[b]
PROBENECID	
Pui (2013) [33]	8/42 patients (19%) with eGFR ≥50 ml/min and 2/15 patients (13%) with eGFR <50 ml/min presented AEs attributed to probenecid, leading to discontinuation of use in 7 of them: gastrointestinal side effects (3), headache (2), rashes (2), painful tongue (1), mouth ulcers (1) and urolithiasis (1) (this patient had a history of kidney stones, and the calculus was not analysed for its composition).
LESINURAD	
Hagerty (2011) [39]	Tolerability and safety of lesinurad were similar in patients with normal and impaired renal function.[b]
Dalbeth (2015) [40] (CRYSTAL)	Cr elevation ≥1.5×: • CrCl ≥90 ml/min: FBX+LESU200 = 5.4%; FBX+LESU400 = 7.1% • CrCl 60–<90 ml/min: FBX+LESU200 = 7.3%; FBX+LESU400 = 15.6% • CrCl 30–<60 ml/min: FBX+LESU200 = 0%; FBX+LESU400 = 4.5% Any adverse event: • CrCl ≥90 ml/min: FBX+LESU200 = 89.2%; FBX+LESU400 = 88.1% • CrCl 60–<90 ml/min: FBX+LESU200 = 68.3%; FBX+LESU400 = 77.8% • CrCl 30–<60 ml/min: FBX+LESU200 = 92.9%; FBX+LESU400 = 81.8%
Saag (2015) [41] (CLEAR 1/CLEAR 2)	Cr elevation ≥1.5×: • CrCl ≥90 ml/min: Allo+LESU200 = 5.5%; Allo+LESU400 = 13.7% • CrCl 60–<90 ml/min: Allo+LESU200 = 6.0%; Allo+LESU400 = 18.5% • CrCl 30–<60 ml/min: Allo+LESU200 = 6.8%; Allo+LESU400 = 12.9% Any adverse event: • CrCl ≥90 ml/min: Allo+LESU200 = 73.6%; Allo+LESU400 = 77.6% • CrCl 60–<90 ml/min: Allo+LESU200 = 68.9%; Allo+LESU400 = 79.8% • CrCl 30–<60 ml/min: Allo+LESU200 = 85.1%; Allo+LESU400 = 81.4%
PEGLOTICASE	
Yood (2014) [44] [GOUT1 (C0405) and GOUT2 (C0406)]	Patients with stage 3 or 4 CKD had no clinically meaningful changes in renal function with ≤6 months of pegloticase therapy. Likewise, no changes in renal function were observed in patients who participated in the long-term open-label extension study for a total mean period of 1.5 years of pegloticase therapy.[b] Gout flares and infusion reactions were the two most common AEs.[b] There were no differences in the pegloticase safety profile based on CKD stage.[b]

AE: adverse event; AHS: allopurinol hypersensitivity syndrome; Allo: allopurinol; APEX: Allopurinol Placebo-Controlled Efficacy Study of Febuxostat; CARES: Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities trial; CKD: chronic kidney disease; CLEAR: Combining Lesinurad with Allopurinol Standard of Care in Inadequate Responders; CONFIRMS: Urate-Lowering Efficacy and Safety of Febuxostat in the Treatment of the Hyperuricaemia of Gout; Cr: creatinine; CrCl: creatinine clearance (in millilitres per minute); CRYSTAL: Combination Treatment Study in Subjects with Subcutaneous Tophaceous Gout with Lesinurad and Febuxostat; eGFR: estimated glomerular filtration rate (in millilitres per minute); FACT: Febuxostat Versus Allopurinol Controlled Trial; FAST: Febuxostat versus Allopurinol Streamlined Trial; FBX: febuxostat; LASSO: Long-term Allopurinol Safety Study Evaluating Outcomes in Gout Patients; LESU: lesinurad; MI: myocardial infarction; SAE: serious adverse event; TEAE: treatment emergent adverse event. [a]References [4, 21–23, 25, 28, 36] do not report adverse events. Studies [13, 15, 18, 20, 24, 27, 29–31, 34, 37, 38, 42, 43] do not report adverse events according to renal function. References [32, 35] reported that there were no adverse events. [b]Statement made by authors. [c]Statement made by authors. Raw data relating to TEAEs according to renal function were not published.

TABLE 3 Studies addressing associations between allopurinol dose, kidney function and allopurinol hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms

First author (year)	Proportion of subjects with gout	Initial allopurinol dose (mg/day)	Data related to CrCl/eGFR (ml/min)	Data related to HLA-B*5801	Results related to diuretic use
Stamp (2012) [50]	100%	Mean 183.5 ± 14 for cases and 112.2 ± 6.3 for controls	Odds of AHS increased as starting dose corrected for GFR increased, for the highest quintile, OR 23.2 ($P < 0.01$)	NR	48% of cases were taking diuretics. Risk of diuretic use not able to be estimated.
Kim (2013) [51]	10.1% of allopurinol initiators	HR for >300 mg *vs* low dose 1.30 (95% CI: 0.31, 5.36)	5.9% of allopurinol initiators had CKD. CKD unadjusted HR 0.72 (95% CI: 0.18, 2.97)	NR	Unadjusted HR for diuretic use 2.10 (95% CI: 1.10, 4.01). Multivariable HR 1.49 (95% CI: 0.77, 2.90)
Yang (2015) [52]	NR. 49.5% of new allopurinol users in 2011 had asymptomatic hyperuricaemia	>100 mg/day *vs* ≤100 mg day OR 1.27 (95% CI: 1.18, 1.37)	OR with renal disease *vs* without 1.49 (95% CI: 1.38, 1.61)	NR	OR for allopurinol hypersensitivity with thiazide use 1.02 (95% CI: 0.78, 1.32)
Chung (2015) [53]	67% of cases	138 (S.D. 75.5) in people with SCAR *vs* 117 (S.D. 43.7) in tolerant controls (*P* 0.078)	Baseline eGFR 34 (S.D. 29.0) in people with SCAR, *vs* 67.5 (S.D. 32.4) in tolerant controls ($P < 0.001$) Dosage/eGFR (mg/ml/min): 8.2 (S.D. 7.6) in people with SCAR *vs* 2.7 (S.D. 3.3) in tolerant controls ($P < 0.001$)	96% of people with SCAR HLA-B*5801 carriers, 17.4% in tolerant controls ($P < 0.001$)	Diuretic usage 31.3% of people with SCAR, 21.7% tolerant controls ($P = 0.240$)
Ng (2016) [54]	NR	NR	OR for any cutaneous ADR eGFR 30–60 *vs* >60 1.3 (95% CI: 0.62, 3.71). eGFR < 30 *vs* >60 OR 4.3 (95% CI: 1.96, 9.62) $P < 0.001$	OR for homozygous for HLA-B*5801 and eGFR <30 ml/min, *vs* no HLA-B*5801 and eGFR >60, 1269.45 (95% CI: 192.3, 15 260.1)	NR
Keller (2018) [55]	40%	Multivariate adjusted RR for dose >100: 1.85 (95% CI: 1.36, 2.51)	Multivariate adjusted RR CKD *vs* no CKD 2.33 (95% CI: 1.44, 3.77). For low-risk ethnicity: CKD and Allo >100 *vs* no CKD and Allo ≤ 100 RR 5.65 (95% CI: 2.10, 15.22). For high-risk ethnicity, CKD and Allo >100 *vs* no CKD and Allo ≤100 RR 9.08 95% CI: (3.58, 22.77)	NR	Diuretic use (RR 1.38, 95% CI: 0.99, 1.92).
Huang (2019) [56]	50.6% (in addition 17.2% had nephrolithiasis)	12.1% ≥300, 17.8% 100< to <300, 70.1% ≤100	eGFR ≥60 17/168 (10.1%) 30 ≤ eGFR <60 64/168 (38.1%) 15 ≤ eGFR <30 55/168 (32.7) eGFR <15 32/168 (19%) Largest number of cases occurred in those with eGFR 15–60 and initial allopurinol dose 100 mg/day	NR	NR

ADR: adverse drug reaction; AHS: allopurinol hypersensitivity syndrome; Allo: allopurinol; CKD: chronic kidney disease; CrCl: creatinine clearance; eGFR: estimated glomerular filtration rate; HR: hazard ratio; NR: not reported; OR: odds ratio; RR: relative risk; SCAR: severe cutaneous adverse reactions.

The two observational studies included were more recent. The first study evaluated the pharmacokinetic and pharmacodynamic effects of adding probenecid to allopurinol in 20 participants over 18 weeks: 4/5 subjects with eGFR of <50 ml/min reached an SU of <5 mg/dl, and all of the 15 subjects with eGFR of ≥50 ml/min achieved an SU of <5 mg/dl [32]. The second study described efficacy and tolerability of probenecid in 57 participants (15 with CKD) over 36 months: 36 and 45% of subjects with eGFR of >50 and 30–50 ml/min, respectively, reached the SU target of <6 mg/dl, but none of the 4 participants with eGFR of <30 ml/min achieved it [33]. In a single study that reported adverse events according to renal function, they were less common among subjects with an eGFR of <50 ml/min, but the small sample size did not allow us to come to a definitive conclusion [33] (Table 2).

Benzbromarone

Studies with analysis based on renal function

Table 1 summarizes the main characteristics of the five studies that reported the efficacy of benzbromarone based upon renal function, of which only one was an RCT. These five studies included a total of 191 participants, but the variability in patients grouping or outcome reporting made a combined analysis impossible.

Given that most studies reported the efficacy as the mean final SU level compared with the mean baseline SU level, it was not possible to determine the percentage of patients who achieved an SU of <6 mg/dl according to the renal function. In the study with the largest sample of benzbromarone users, Stamp *et al.* [38] concluded that there was no statistically significant difference in the number of patients who achieved an SU of <6.0 mg/dl based on eGFR. None of the included studies reported adverse events according to renal function (Table 2).

Study without analysis based upon renal function

The main characteristics of the only study identified that included participants with CKD taking benzbromarone but did not have an analysis of efficacy and/or safety according to renal function are summarized in Supplementary Table S2, available at *Rheumatology Advances in Practice* online.

Lesinurad

Studies with analysis based on renal function

Table 1 summarizes the main characteristics of the five studies that reported the efficacy of lesinurad based upon renal function. All of these studies excluded subjects with an eGFR of <30 ml/min. Hagerty *et al.* [39] reported two phase 2b studies, which were the only studies in Table 1 to evaluate lesinurad in monotherapy and at doses >400 mg/day, with a maximum lesinurad daily dose of 600 mg. CLEAR (Combining Lesinurad with Allopurinol Standard of Care in Inadequate Responders) 1 and CLEAR 2 were RCTs comparing allopurinol monotherapy and the combination of allopurinol and two doses of lesinurad. They were reported individually as full papers in 2017 [42, 43], but the efficacy data analysed according to the renal function were described in more detail in an ACR abstract in 2015 [41]. The CRYSTAL (Combination Treatment Study in Subjects with Subcutaneous Tophaceous Gout with Lesinurad and Febuxostat) study compared febuxostat in monotherapy with the combination of febuxostat with two lesinurad doses for subjects with tophaceous gout, and the primary efficacy endpoint was an SU of <5 mg/dl, whereas the other studies considered an SU level of <6 mg/dl. The results from the CRYSTAL study based on renal function were reported in a conference abstract [40], and the full-text article was published in 2017 without the detailed data on renal function [62]. These five studies included a total of 1343 participants, with ≥194 subjects presenting eGFR of 30–<60 ml/min.

Only three articles reported safety according to renal function, and results indicate a similar safety profile in patients with normal or mildly impaired renal function; an increased frequency of adverse events was seen in groups using higher doses of lesinurad (400 mg/day), regardless of kidney function (Table 2).

Studies without analysis based upon renal function

Two studies included participants with varying degrees of renal impairment but did not analyse efficacy and/or safety based on renal function. A summary of the characteristics of these studies is shown in Supplementary Table S2, available at *Rheumatology Advances in Practice* online.

Pegloticase

Studies with analysis based on renal function

The main characteristics of the only study that reported efficacy data based on renal function are presented in Table 1. The study was a *post hoc* subgroup analysis of two RCTs and their open-label extension study, including 211 patients with varying degrees of renal dysfunction [44]. The efficacy endpoint was an SU of <6 mg/dl for 80% of the time during months 3 and 6. Overall, there did not appear to be significant differences in efficacy based on renal function. Gout flare and infusion reactions were the most commonly reported adverse events, and there were no differences in the pegloticase safety profile according to renal function (Table 2).

Studies without analysis based upon renal function

Six identified studies included participants with CKD but did not have efficacy and/or safety analyses according to renal function. The main characteristics of these studies are summarized in Supplementary Table S2, available at *Rheumatology Advances in Practice* online.

Discussion

This systematic review found that there is a paucity of data, particularly studies with appropriate methodological quality, on ULTs for subjects with gout and CKD.

There are more data for allopurinol than for the other ULTs, but there was substantial variability in study design, and quantitative meta-analysis was not appropriate. Despite the large number of studies on allopurinol, only 12 studies analysed participants stratified by renal function. Pre-specified and actual doses of allopurinol prescribed were variable, with many studies specifying a maximum dose of 300 mg/day; a dose currently known to be insufficient for most people with gout to achieve the SU target. It is disappointing that given the paucity of data, even when many studies enrolled participants with an eGFR of <60 ml/min/1.73 m^2, the results were not analysed based on renal function. The results of this review do not provide enough data to support or refute current recommendations in guidelines regarding the dosing of ULTs based on renal function [63].

Older uricosurics, such as probenecid and benzbromarone, have scant evidence, largely generated at a time when reporting based on CKD categories was not standardized. There was response in an important proportion of patients, but the safety signals (more concerning for benzbromarone than for probenecid) were difficult to analyse based on kidney function because of lack of stratification on this variable in all but one study with probenecid.

With the newer ULTs, such as febuxostat and lesinurad, the phase 3 clinical trials for US Food and Drug Administration and European Medicines Agency approval have typically excluded people with severely impaired kidney function (eGFR of <30 ml/min/1.73 m^2). Thus, data in this group of people with difficult-to-treat gout are most limited and rely on post-marketing case series and investigator-led studies.

One of the strengths of this study is that it focused on a clearly defined group of people with gout. Many studies of allopurinol and other urate-lowering agents involve participants who receive them for indications other than gout, such as asymptomatic hyperuricaemia. It is difficult to draw conclusions from such studies about the efficacy and safety of allopurinol when used for gout. This is particularly important given that there is some evidence that people with asymptomatic hyperuricaemia treated with allopurinol might be at increased risk of AHS [52].

Limitations of this review include the inability to undertake a meta-analysis of the efficacy of ULTs in individuals with gout and CKD. We did not include people with renal transplants, and our conclusions do not apply to that specific population. We did not include other outcome measures for efficacy, such as a reduction in the size or number of tophi or a decrease in gout flares, both of which occur secondarily to achieving the SU target. Another limitation was the restriction of the searches to the English language, especially considering that benzbromarone is not approved in the USA and many other English-speaking countries, but is used in other non-English-speaking countries. However, this limitation does not seem to yield a significant loss of potentially includable manuscripts. Risk of bias of the included studies was not assessed formally. Few of the included studies aimed specifically to address the issue of efficacy and safety of ULT according to different levels of renal function. In addition, variability in the design of the included studies and diverse methods for reporting outcome data for serum urate limit the conclusions that can be drawn from these studies as a whole, and a formal risk of bias assessment would not alter this.

In conclusion, this is a comprehensive systematic review highlighting the paucity of efficacy and safety data for ULT use to treat gout in the context of CKD. Considering that this association is frequent and permeated by clinical concerns mainly related to safety, such as drug toxicity and polypharmacy interaction, it is crucial that current and future studies include patients with CKD and report results stratified by renal function. Currently, clinicians treating gout in patients with CKD and major professional societies do not have evidence to make informed recommendations on management of this population.

Supplementary data

Supplementary data are available at *Rheumatology Advances in Practice* online.

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Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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