Drugs & Therapy Perspectives (2019) 35:24–28
https://doi.org/10.1007/s40267-018-0568-1

DISEASE MANAGEMENT

Be cautious when treating gout in patients with renal impairment

Adis Medical Writers[1]

Published online: 23 October 2018

Abstract
Gout and renal impairment are frequent comorbidities, with both conditions strongly associated with hyperuricaemia. The management of gout involves treating and preventing gout flares, and reducing serum urate levels to eliminate the urate crystal deposits in the joints. Although the overall treatment of gout is very similar in patients with or without renal impairment, special precautions must be taken to avoid adverse effects related to renal impairment.

Gout is fully curable …

Gout is characterized by monosodium urate (MSU) crystal deposits in the joint that trigger an inflammatory response, producing episodes of intense pain and swelling [1]. The development of MSU crystal deposits is silent and potentially very prolonged; diagnosing gout before the first gout attack by screening for the crystals is currently difficult [2]. Nevertheless, MSU crystal formation is fully reversible and gout, therefore, is considered a curable disease [3].

Gout treatment and prevention strategies in patients with renal impairment must be approached carefully due to the complexity of renal impairment, and drug selection, dosage modification and the impact of the treatment on the existing renal impairment should be considered [4]. This article provides a summary of the treatment and management of gout in patients with renal impairment, as reviewed by Pascual et al. [4].

… and often co-exists with renal impairment

MSU crystal deposits form and persist with prolonged hyperuricaemia, which occurs most often from insufficient serum urate (SU) elimination [1]; as such, renal impairment contributes greatly to the development of gout [4]. However, hyperuricaemia may also contribute to renal impairment, with multiple studies showing a positive correlation between SU levels and the risk of kidney disease [4]; similarly, patients with gout have a greater risk of end-stage renal disease (ESRD) [5].

Gout treatment in patients with renal impairment, therefore, requires particular caution in terms of selecting the best treatment at the most appropriate dosage [4]. Creatinine clearance (Cr_{CL}) should be assessed beforehand in order to select the most appropriate drug and dosage [4].

Focus on lowering serum urate …

At the emergence of gout symptoms, treatment to eliminate MSU crystal deposits should be administered until all signs of gout are cleared and, if necessary, continued during treatment and prophylaxis for gout flares (Fig. 1) [4]. As MSU crystals dissolve completely at normal SU levels, the primary aim of gout treatment is to lower SU levels, typically with SU-lowering drugs (Table 1) [4]. Such treatment decreases the risk of gout flares, often without the need for additional prophylactic treatments [4].

SU levels should be reduced to < 0.30 mmol/L (< 5 mg/dL) in patients with severe gout [3]. Although MSU crystals dissolve faster when SU levels at low, lowering SU to < 0.18 mmol/L (< 3 mg/dL) for a period of years is advised against due to a possible increased risk of neurological disorders [3]. It is difficult to determine when MSU crystals have been fully dissolved, and ultrasounds may be useful in identifying any remaining deposits [4]. Once the deposits have been dissolved, SU levels should be maintained at < 0.36 mmol/L (< 6 mg/dL), the level at which new crystals cannot form [6].

✉ Adis Medical Writers
dtp@adis.com

[1] Springer, Private Bag 65901, Mairangi Bay, 0754 Auckland, New Zealand

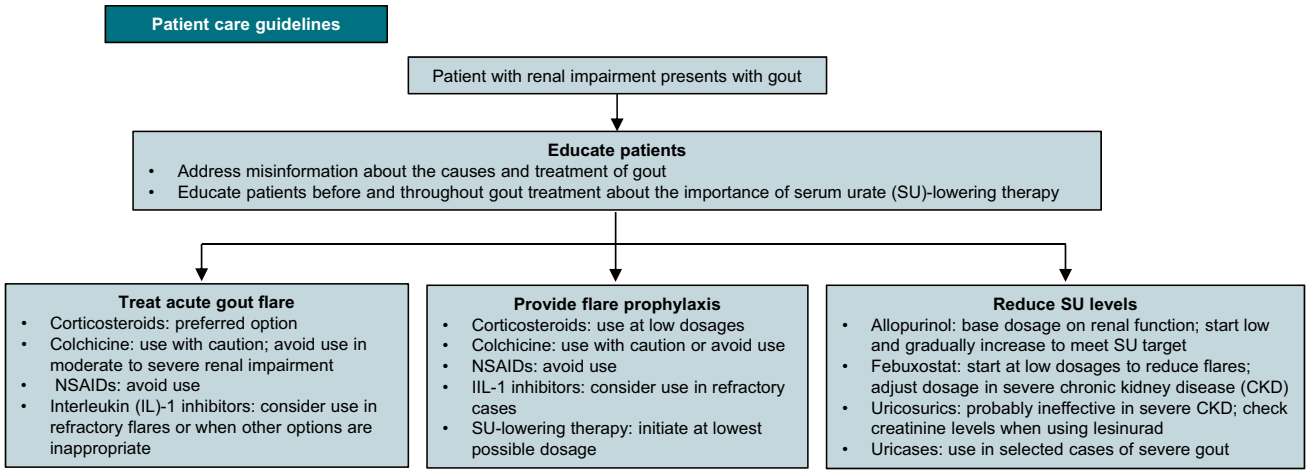

Fig. 1 Treating gout in patients with renal impairment, as suggested by Pascual et al. [4]

… but start slow

In general, it is crucial to slowly ease into SU reduction therapy; gout flares are more likely (and at greater severity) if SU levels drop too sharply at the beginning of treatment [4]. Starting treatment with SU-lowering drugs at lower dosages (which can be gradually increased as appropriate) is particularly imperative for gout patients with renal impairment due to the potential for kidney-related adverse effects to occur (Table 1) [4].

Allopurinol and febuxostat are xanthine-oxidase inhibitors, and are the drugs most commonly used to treat hyperuricaemia (Table 1) [4]. If xanthine-oxidase inhibitor monotherapy is unable to adequately reduce SU levels, a uricosuric drug may be added to reduce MSU crystal formation and improve excretion of SU (Table 1) [4], especially in patients with severe gout and limited treatment options [7]. Uricosuric drugs may be less effective in lowering SU levels as renal impairment worsens [4]. Uricase and pegloticase (Table 1), are highly effective in reducing SU levels, but are associated with high immunogenicity [8]. Their use should be limited to the treatment of selected severe cases [4].

If necessary, haemodialysis is a highly effective in removing SU and may also clear tophi [4]. However, as sudden drops in SU may trigger gout attacks, post-dialysis SU levels should be examined before administering SU-lowering drugs, which should typically be administered at lower dosages in patients undergoing haemodialysis [4].

Address gout flares with caution

Untreated gout flares generally subside within 2 weeks [4]. Colchicine is an effective treatment for gout flares in patients with normal renal function, but its use has been discouraged in those with renal impairment (Table 2). Exposure to colchicine increases in patients with moderate to severe renal impairment [14], leading to a greater risk of colchicine-related toxicity [15]. Oral, parenteral and intra-articular corticosteroids seem to be a safe and effective alternative to colchicine in this population (Table 2), but their use in certain patients is contraindicated, not recommended or requires caution [4].

With interleukin (IL)-1 activation being the trigger for gout-related inflammation, the anti-IL-1 agents canakinumab and anakinra are also effective in gout patients with renal impairment (Table 2) [4]. For example, used on-demand to treat and prevent gout flares, subcutaneous canakinumab 150 mg was more effective than on-demand intramuscular triamcinolone acetonide 40 mg [16], and a single dose of canakinumab $\geq$ 50 mg was more effective than daily colchicine 0.5 mg as prophylaxis [17].

Importantly, despite the general effectiveness of NSAIDs in treatment gout flares and as prophylaxis, they should not be used to treat gout in patients with renal impairment [4].

Evidence suggests that prophylaxis should continue for $>$ 6 months, although the optimal duration of prophylaxis not yet clear [4]. In more severe cases, such as frequently flaring

Table 1 Gout treatment drugs to lower serum urate levels in patietns with impaired renal function, based on a review by Pascual et al. [4]

Treatment	Comments
Xanthine-oxidase inhibitors (↓ the amount of uric acid formed)	
Allopurinol	Mainstay of gout treatment
	Oxypurinol (active metabolite of allopurinol) is largely excreted unchanged by the kidneys; $t_{1/2} < 30$ h in patients with normal renal function, but up to 1 week in those with severe renal impairment; may accumulate in patients with $Cr_{CL} < 10$ mL/min as it undergoes virtually no renal clearance
	Starting dosage in patients with $Cr_{CL} < 60$ mL/min: ≤ 50 mg/day (to ↓ risk of AHS)
	Basing maintenance dosages on Cr_{CL} is an out-dated practice, and often leads to under-treatment
	Instead, slowly ↑ dosage to meet SU target (i.e. < 0.36 mmol/L; < 6 mg/dL) to a maximum of 900 mg/day
	Risk of developing AHS is ↑ in patients with renal impairment or receiving thiazide diuretics [9], or with the *HLA-B*58:0a* allele (most commonly found in Asian subpopulation, notably in individuals of Korean, Thai or Han Chinese descent) [10]
Febuxostat	Predominantly undergoes hepatic metabolism (≈ 70%), allowing adequate ↓ of SU levels in patients with renal impairment
	Start with low dosage [40 (USA) or 80 (Europe) mg/day]; ↑ to 80 (USA) or 120 (Europe) mg/day if necessary
	Maintains its efficacy and safety in patients with Cr_{CL} as low as 15 mL/min; however, as the proper dosage in patients with severe renal impairment has not been determined, caution is required in patients with advanced CKD
	Patients with pre-existing co-morbid major CV conditions: may ↑ risk of all-cause and CV mortality, but not the rate of adverse CV events, relative to allopurinol [11]
Uricosuric drugs (↓ the tubular reabsorption of uric acid, thereby ↑ its renal clearance)	
Benzbromarone[a]	Highly potent urate transporter 1 inhibitor; associated with severe hepatotoxicity
	Dosage range: 50–200 mg/day
	Do not use if $Cr_{CL} < 20$ mL/min; dosage adjustment is not required in patient with lower levels of renal impairment as the drug primarily undergoes faecal excretion
	Use is not recommended in patients with $Cr_{CL} < 20$ mL/min
Probenecid[a]	Do not use if $Cr_{CL} < 30$ mL/min; use with caution in other patients with renal impairment
	Usual dosage: 250 mg twice daily for 1 week, then ↑ to 500 mg twice daily; if necessary to achieve target SU levels, ↑ in 500 mg increments every 4 weeks as tolerated to a maximum of 2 g/day
	May use in combination with an xanthine-oxidase inhibitor
Sulfinpyrazone[a]	Start at a dosage of 50 mg twice daily and gradually ↑ up to 200–400 mg in two divided doses
Lesinurad[a]	Use only in combination with a xanthine-oxidase inhibitor (in patients with gout refractory to adequate doses of a prior xanthine-oxidase inhibitor); do not use as monotherapy due to tolerability issues
	Maximum dosage 200 mg/day (safety concerns regarding higher dosages)
	Dosage adjustment not required in patients with mild to moderate renal impairment, but use with caution
	May ↑ serum creatinine levels, but effects appears to be largely reversible
Uricases (transform uric acid to allantoin thereby ↓ uricaemia)	
Uricase and pegloticase	Sharply ↓ uricaemia by transforming uric acid to allantoin, which is more readily eliminated [12]
	May be effective when used in combination with a xanthine-oxidase inhibitor + a uricosuric [13]
	Limitations: high rates of immunogenicity, adverse infusion reactions, risk of anaphylaxis and limited availability of pegloticase

Consider the contraindications, precautions and warnings associated with the use of each drug before initiating treatment

AHS allopurinol hypersensitivity syndrome, *CKD* chronic kidney disease, Cr_{CL} creatinine clearance, *CV* cardiovascular, *HLA-B* human leukocyte antigen B, *SU* serum urate, ↑ increase(s/d/ing), ↓ reduce(s/ing)/reduction

[a]Not widely available

severe gout, combination therapy with multiple drugs (e.g. colchicine + a corticosteroid) may be temporarily required [4].

Educate to improve treatment adherence

Patients should be thoroughly educated about gout and its treatment, and any misconceptions about the condition should be addressed [4]. Proper education may improve adherence to gout treatment. For example, in patients with gout who received individualized education, 90% were adherent to gout treatment after 5 years, with 85% of these taking their prescribed medication ≥ 6 days a week [22].

Take home messages

When managing gout in patients with renal impairment:

- Consider the renal function of the patient, and select the best treatment at the most appropriate dosage.

Table 2 Treatment and prevention of gout flares in individuals with renal impairment, based on a review by Pascual et al. [4]

Drug	Comments
Corticosteroids	
Oral	Regular flares: administer a dosage equivalent to prednisone 30 mg × 1 or 2 days, then 20 mg × 1 day, then 10 mg × 2–4 days
	Severe polyarticular gout flares or flares of long duration: treatment for a full 15 days may be required
	To prevent rebound flares after stopping corticosteroid, co-administer with prophylactic colchicine from the first day or use a low corticosteroid dosage (equivalent to prednisone 5 or 7.5 mg/day) for a few extra days
	Avoid prolonged use as prophylactic; no specific problem for patients with renal impairment when used at low doses (equivalent to prednisone 5–10 mg/day) for longer durations
	As prophylaxis, always use with SU-lowering treatment to ↓ risk of flares and minimize prophylaxis duration
Intramuscular	40–60 mg triamcinolone acetonide; can follow with intramuscular prednisone/prednisolone, especially in patients unable to take oral medications [18]
Intra-articular	Highly effective and convenient when only a few accessible joints are inflamed
	If total dose is a concern, administer smaller doses of triamcinolone acetonide adjusted to the joint size [19]
	Use with mepivacaine provides very rapid pain relief that may persist after the anaesthetic effects wear off [20]
Anti-interleukin-1 agents	
Canakinumab	Effective in complex or refractory situations
	Especially appropriate for gout flare relief in patients with renal impairment and unstable diabetes
	Long lasting; prevents new flares from occurring over a prolonged period of time
	Consider use in difficult cases where alternatives are considered inappropriate
	High acquisition cost
Anakinra	Not approved to treat/prevent gout flares, but evidence suggests it may be effective
	May be cost effective, as only a few doses are usually required
Colchicine	Use lower than normal dosages or avoid use in patients with renal impairment
	Adjust dosage according to Cr_{CL} (e.g. 0.5/0.6 mg twice daily for $Cr_{CL} \geq 50$ mL/min; 0.5/0.6 mg once daily for Cr_{CL} 35–49 mL/min; 0.5/0.6 mg every 2–3 days for Cr_{CL} 10–34 mL/min; dosage of 0.5 or 0.6 mg depends on which dosage strength is locally available); do not use if $Cr_{CL} < 10$ mL/min [21]
	Not approved for prophylaxis of gout flare in some countries

Consider the contraindications, precautions and warnings associated with the use of each drug before initiating treatment

Cr_{CL} creatinine clearance, *SU* serum urate, ↓ reduce(s/d)/reduction

- Titrate allopurinol dosages to achieve target SU levels (outdated practice to base dosage on Cr_{CL}).
- Avoid or use low dosages of colchicine.
- Be aware that many uricosuric drugs are not widely available, and may be of limited effectiveness in this patient population.
- Educate patients about gout and its treatment to improve treatment adherence.

Compliance with ethical standards

Conflict of interest The article was adapted from *Drugs & Aging* 2018;35(4):263–73 [4] by employees of Adis/Springer, who are responsible for the article content and declare no conflicts of interest.

Funding The preparation of this review was not supported by any external funding.

References

1. Chen LX, Schumacher HR. Gout: an evidence-based review. J Clin Rheumatol. 2008;14(5 Suppl):S55–62.
2. Newberry SJ, FitzGerald JD, Motala A, et al. Diagnosis of gout: a systematic review in support of an American College of Physicians Clinical Practice guideline. Ann Intern Med. 2017;166(1):27–36.
3. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis. 2017;76(1):29–42.
4. Pascual E, Sivera F, Andrés M. Managing gout in the patient with renal impairment. Drugs Aging. 2018;35(4):263–73.
5. Yu KH, Kuo CF, Luo SF, et al. Risk of end-stage renal disease associated with gout: a nationwide population study. Arthritis Res Ther. 2012;14(2):R83.
6. Perez-Ruiz F, Calabozo M, Herrero-Beites AM, et al. Improvement of renal function in patients with chronic gout after proper control of hyperuricemia and gouty bouts. Nephron. 2000;86(3):287–91.
7. Reinders MK, van Roon EN, Jansen TL, et al. Efficacy and tolerability of urate-lowering drugs in gout: a randomised controlled

trial of benzbromarone versus probenecid after failure of allopurinol. Ann Rheum Dis. 2009;68(1):51–6.
8. Yang X, Yuan Y, Zhang CG, et al. Uricases as therapeutic agents to treat refractory gout: current states and future directions. Drug Dev Res. 2012;73(2):66–72.
9. Chao J, Terkeltaub RA. Critical reappraisal of allopurinol dosing, safety, and efficacy for hyperuricemia in gout. Curr Rheumatol Rep. 2009;11:1135–40.
10. Saito Y, Stamp LK, Caudle KE, Hershfield MS, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for human leukocyte antigen B (HLA-B) genotype and allopurinol dosing: 2015 update. Clin Pharmacol Ther. 2015;99(1):36–7.
11. White WB, Saag KG, Becker MA, et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. N Engl J Med. 2018;378(13):1200–10.
12. Pui CH. Rasburicase: a potent uricolytic agent. Expert Opin Pharmacother. 2002;3(4):433–42.
13. Mejia-Chew C, Torres RJ, de Miguel E, et al. Resolution of massive tophaceous gout with three urate-lowering drugs. Am J Med. 2013;126(11):e9–10.
14. Wason S, Mount D, Faulkner R. Single-dose, open-label study of the differences in pharmacokinetics of colchicine in subjects with renal impairment, including end-stage renal disease. Clin Drug Investig. 2014;34(12):845–55.
15. Bardin T, Richette P. Impact of comorbidities on gout and hyperuricaemia: an update on prevalence and treatment options. BMC Med. 2017;15(1):123.
16. Lyseng-Williamson KA. Canakinumab: a guide to its use in acute gouty arthritis flares. BioDrugs. 2013;27(4):401–6.
17. Schlesinger N, Mysler E, Lin HY, et al. Canakinumab reduces the risk of acute gouty arthritis flares during initiation of allopurinol treatment: results of a double-blind, randomised study. Ann Rheum Dis. 2011;70(7):1264–71.
18. Khanna D, Khanna PP, Fitzgerald JD, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res. 2012;64(10):1447–61.
19. Fernandez C, Noguera R, Gonzalez JA, et al. Treatment of acute attacks of gout with a small dose of intraarticular triamcinolone acetonide. J Rheumatol. 1999;26(10):2285–6.
20. Andrés M, Begazo A, Sivera F, et al. Intraarticular triamcinolone plus mepivacaine provides a rapid and sustained relief for acute gouty arthritis [abstract no. AB0815]. Ann Rheum Dis. 2016;75:1182.
21. Terkeltaub RA. Clinical practice: gout. N Engl J Med. 2003;349(17):1647–55.
22. Rees F, Jenkins W, Doherty M. Patients with gout adhere to curative treatment if informed appropriately: proof-of-concept observational study. Ann Rheum Dis. 2013;72(6):826–30.