Major unanswered questions in the clinical gout field

Lisa K. Stamp

Purpose of review
Although gout is one of the most common forms of inflammatory arthritis, it has been relatively neglected until recently. Despite progress in many areas of pathophysiology and genetics of gout and the development of new urate lowering therapies, there remain a number of unanswered clinical questions. With the resurgence of interest in gout it is important to recognize key aspects of gout management that remain challenging and require further research.

Recent findings
The unanswered clinical issues outlined in this review are basic aspects of gout management that clinicians treating people with gout face on a daily basis and include when urate lowering therapy should be commenced, the most appropriate target serum urate, use of prophylaxis when starting urate lowering therapy and the most appropriate urate lowering therapy, particularly for those with chronic kidney disease.

Summary
Some of the issues outlined in this article are the subject of ongoing clinical research and some, such as use of allopurinol in people with chronic kidney impairment, may be less relevant with the advent of potentially safer urate lowering therapies but until that time further understanding to aid clinical decision-making is required.

Keywords
gout, management, prophylaxis, urate, urate lowering therapy

INTRODUCTION

Gout has been recognized since ancient times but until recently has been relatively a neglected disease by physicians, researchers, pharmaceutical developers and indeed by many people with gout. The last 5–10 year period has seen a resurgence of interest in gout with advances in the understanding of the pathophysiology, genetics and outcomes of gout as well as the emergence of new urate lowering therapies. Despite these advances, the quality of care remains generally poor. A number of clinical questions remain unanswered (Table 1), and some of these are reflected by differences in gout management guidelines (summarized in Table 2). This review will discuss some of the key unanswered clinical questions that may change clinical practice with appropriate evidence.

Target serum urate

The aim of long-term gout therapy is to lower serum urate sufficiently to allow dissolution of monosodium urate crystals. OMERACT identified serum urate as a mandatory outcome measure in chronic gout studies [4], and serum urate is a key outcome measure in clinical trials of urate lowing therapies. However, there is variability in current recommendations about the appropriate target urate. Both ACR and EULAR recommend a target urate of less than 6 mg/dl for all people with gout [3▪▪,5], whereas the British Society of Rheumatology recommends the lower target of less than 5 mg/dl for all [1]. This lower target is recommended for those with tophi by ACR [5] and EULAR [3▪▪].

These target urate recommendations make the assumption that serum urate is a 'biomarker' for important clinical outcomes in people with gout such as attacks and tophus reduction. Although

Department of Medicine, University of Otago, Christchurch, New Zealand

Correspondence to Professor Lisa K. Stamp, Department of Medicine, University of Otago, Christchurch, PO Box 4345, Christchurch 8140, New Zealand. Tel: +64 3 364 0253; fax: +64 3 364 0935; e-mail: lisa.stamp@cdhb.health.nz

Curr Opin Rheumatol 2017, 29:171–177
DOI:10.1097/BOR.0000000000000367

KEY POINTS

- Urate lowering therapy in people with gout and chronic kidney disease remains controversial, and the most effective and safest way to achieve target urate needs to be clarified.
- There are a number of unanswered questions with regard target serum urate including the most appropriate target and duration for which it must be maintained.
- Effective mechanisms for delivery of urate lowering therapy healthcare professionals and uptake by people with gout are required to improve clinical outcomes.

serum urate fulfils many criteria of a biomarker [6], there is less evidence specifically linking urate and/or different urate targets to important clinical outcomes. Lowering serum urate has been associated with disappearance of monosodium urate crystals from synovial fluid of people with gout [7]. There is a linear relationship between mean serum urate and velocity of tophi reduction with lower urate associated with faster reduction in tophi [8] and in clinical trials of pegloticase individuals who maintain serum urate less than 6 mg/dl for at least 80% of the time were more likely to have complete remission of tophus at 6 months [9]. The frequency of gout flares reduces over time in people achieving target urate [10,11] and in a post-hoc analysis of the FACT study, the proportion of patients with gout flare between weeks 49 and 52 was lower among those with post-baseline serum urate (SU) less than 6 mg/dl than those with postbaseline SU at least 6 mg/dl (6 vs. 14%; $P = 0.005$) [12].

To date, the majority of clinical trials of urate lowering therapies have used serum urate as the primary efficacy outcome measure. Although these studies indicate that reduction in serum urate is associated with some clinical benefits, they do not accurately identify whether one particular target is superior to another. There are no head-to-head randomized controlled trials comparing clinical outcomes with different serum urate targets. Whether a target urate of less than 5 mg/dl is

Table 1. Key unanswered clinical questions in gout

When to commence urate lowering therapy	What proportion and when do people with asymptomatic monosodium urate crystal progress to symptomatic gout?
	Is asymptomatic deposition of monosodium urate crystals an indication for urate lowering therapy?
Target urate	What is the most appropriate target urate to improve patient centred outcomes such as gout flares and tophi?
	Is serum urate a 'biomarker' for patient-centred outcomes such as gout flares and tophi?
	How long does target urate need to be maintained – can we move to a remission induction/maintenance protocol?
	Is a sustained low serum urate associated with risk of neurodegenerative disorders and what is the acceptable long-term urate target to balance risks and benefits of urate lowering in this regard?
Prophylaxis when starting urate lowering	Are newer gradual urate lowering therapy dose escalation strategies associated with fewer gout flares and therefore reduced need for prophylaxis?
	Can use of prophylaxis be tailored based on clinical characteristics such as baseline urate or presence of tophi rather than used in a one-size-fits all manner?
	What is the optimal duration of prophylaxis?
Urate lowering therapy in people with gout and chronic kidney disease	What is the safest and most effective strategy for urate lowering therapy in people with gout and chronic kidney disease?
	Is increasing allopurinol above creatinine-clearance-based doses associated with an increased risk of severe cutaneous adverse reactions in people who have commenced and tolerated therapy during the high-risk period for severe cutaneous adverse reactions?
	Is febuxostat also rarely associated with severe cutaneous adverse reactions and how is this risk related to allopurinol reactions?
Dietary and lifestyle advice	Does dietary modification provide significant benefit for people with gout?
	What is the role of complementary therapies in management of gout?
Healthcare delivery for people with gout	What are the most effective strategies for improving initiation and adherence of urate lowering therapy and the treat-to-target urate approach in people with gout?

Table 2. Comparison of key difference in international guidelines for management of gout which highlight areas of clinical uncertainty

	BSR 2007 guidelines [1]	ACR 2012 guidelines [2]	EULAR 2016 guidelines [3▪▪]
Target SU	<5 mg/dl for all	<6 mg/dl minimum for all	<6 mg/dl for all
		For severe or tophaceous disease may need <5 mg/dl (0.30 mmol/l)	For severe gout (tophi, frequent attacks and chronic arthropathy) <5 mg/dl (0.30 mmol/l)
			SU < 3 mg/dl (0.18 mmol/l) not recommended for long-term
Prophylaxis during ULT initiation	First line – colchicine for up to 6 months	First line – colchicine	First line – colchicine or NSAID
	Second line – NSAID but limit duration to 6 weeks	Second line – NSAID	Duration 6 months
		Duration the greatest of – at least 6 months or 3 months after achieving target SU if no tophi or 6 months after achieving target if tophi present	Acknowledge that not all people may require prophylaxis and discussion with patient recommended
Allopurinol dosing in chronic kidney disease	Starting dose of 50–100 mg/day with gradual escalation, adjusted if necessary for renal function, until the target urate or maximum dose of 900 mg is reached	Maximum starting dose 100 mg/day for any patient with a lower dose of 50 mg/day in those with chronic kidney disease ≥stage 4	No starting dose recommended
		Gradual dose escalation to achieve target urate with doses above 300 mg daily even in those with chronic kidney impairment	Maximum dose adjusted to creatinine clearance and if target not achieved switch to febuxostat or benzbromarone with or without allopurinol (expect in patients with eGFR < 30 ml/min)
Dietary and lifestyle advice	Avoid 'crash dieting', high protein/low carbohydrate diets, liver, kidneys, shellfish and yeast extracts	Avoid offal, high fructose corn-syrup sweetened beverages/foods, excess alcohol	Avoidance of alcohol, sugar sweetened beverage, heavy meals and excessive intake of meat and seafood
	Limit high purine foods, red meat, overall protein intake and alcohol consumption should	Limit meat and seafood, fruit juices, sugar sweetened beverages, alcohol, table sugar and salt	
	Encourage skimmed milk and/or low-fat yoghurt, soy beans	Encourage low-fat/nonfat dairy and vegetables	Encourage low-fat dairy
	Dietary modification to achieve ideal body weight should be attempted	Weight loss in obese to achieve BMI that promotes general health	Weight loss if appropriate

eGFR, estimated glomerular filtration rate; SU, serum urate; ULT, urate lowering therapy.

superior to less than 6 mg/dl or less than point of saturation has not been systematically examined.

Another key clinical question is how long 'target' urate should be maintained. The target of less than 6 mg/dl, which is well below saturation point at physiological temperature and pH, provides a margin to allow for normal fluctuations of urate while remaining below target. This may be necessary until the crystal burden has dissolved, and gout attacks have ceased, that is 'remission induction'. Whether the target can then be 'relaxed' to a higher level over the longer term, that is 'maintenance', without recurrence of symptoms remains unknown. Complete withdrawal of urate lowering therapy in people who have achieved sustained reduction in serum urate has been associated with prolonged periods before recurrence of gout symptoms [13] suggesting that life-long therapy is required to prevent recurrence. The EULAR recommendations specifically state serum urate should not be sustained at levels less than 3 mg/dl for the long term (several years), rather until total crystal dissolution and resolution of gout has been achieved [3▪▪]. This is based on observational studies linking urate and

neurodegenerative disorders such as Parkinson's disease [14]. Whether long-term urate lowering increases the risk of neurodegenerative disorders is unknown and the optimal serum urate to balance the risk of gout and neurological disorders remains to be determined.

Prophylaxis when starting urate lowering therapy

Prophylaxis against flares is recommended when starting urate lowering therapy (Table 2) [2,3▪▪]. The rationale for prophylaxis is based on an increased gout flare rate after introduction of urate lowering therapy. In the 52-week FACT study of febuxostat 80 or 120 mg daily vs. allopurinol 300 mg daily, all participants received prophylaxis with either colchicine 0.6 mg daily or naproxen 250 mg twice daily for the first 8 weeks. During this initial 8-week period, a significantly greater proportion of those receiving febuxostat 120 mg required treatment for a gout flare than those receiving febuxostat 80 mg or allopurinol 300 mg [12]. Significantly, more participants achieved serum urate less than 6 mg/dl by week 2 in those who received febuxostat 120 mg compared with febuxostat 80 mg and compared with allopurinol suggesting that there may be an association between rate of urate reduction and flare rate. The slower reduction in serum urate may, therefore, be associated with fewer gout flares. It is now generally recommended that urate lowering therapy be started at low dose and slowly increased, an approach, which lowers urate more gradually and may therefore be associated with a lower flare rate and thus less need for prophylaxis. Many people with gout would prefer not to have to take prophylaxis when commencing urate lowering and preliminary evidence suggests that this slow dose escalation approach may not be associated with an increase in flare rate [15].

Few clinical trials specifically examine the risks and benefits of prophylaxis when commencing urate lowering therapy. Borstad *et al.* [16] showed fewer people who received colchicine 0.6 mg twice daily had gout flares compared with placebo (33 vs. 77% $P = 0.008$) when commencing allopurinol, although significantly more of those who received colchicine had diarrhoea compared with placebo (38 vs. 4.5%; $P = 0.009$). Careful examination of variables associated with a higher flare rate and high burden of urate such as tophi and baseline serum urate will be required to determine, whether all people with gout commencing urate lowering therapy require prophylaxis, or whether this can be modified based on the clinical characteristics, urate lowering drug and starting regimen.

The optimal duration of prophylaxis also requires further investigation. The current 6-month duration is based on data from recent clinical trials of febuxostat where prophylaxis with colchicine or NSAID for up to 6 months was superior to 8 weeks with no increase in adverse effects [17]. Whether there is a specific duration of prophylaxis, or whether duration should be determined by clinical variables such as tophi and serum urate, or combination of these has not been systematically examined. Consideration of the adverse effects, cost effectiveness and impact on adherence with urate lowering therapy, as well as the flare rates will allow clinicians, and people with gout to make more informed decisions about the use of prophylaxis using newer urate lowering therapy dosing strategies.

Urate lowering therapy in chronic kidney disease

Management of gout, in particular use of allopurinol, in people with chronic kidney disease remains controversial. This has been highlighted recently by differences in the American and European Gout guidelines with respect to allopurinol dosing (Table 2). Given the low cost and wide spread availability of allopurinol, whether it can be used effectively *and* safely is a key clinical question particularly in areas where newer more expensive drugs may not be available.

Chronic kidney impairment is one of a number of risk factors for the rare but potentially fatal severe cutaneous adverse reactions associated with allopurinol (including allopurinol hypersensitivity syndrome, toxic epidermal necrolysis and Stevens–Johnson Syndrome) [18,19]. These adverse reactions tend to occur in the early weeks to months after commencing allopurinol, and other risk factors include higher starting allopurinol dose, diuretics and the presence of HLA-B*5801 [20]. Individuals who develop these severe adverse reactions who have chronic kidney disease have a poorer outcome [21▪▪]. The observed association with chronic kidney disease led to publication of creatinine-clearance-based dosing guidelines which have been widely followed and continue to be recommended by EULAR [22]. However, the majority of people fail to achieve target urate on these restrictive doses [23] and either dose escalation above creatinine-clearance-based doses or switching to an alternative urate lowering agent is required to achieve target urate.

When considering the risk of these severe cutaneous reactions, it is important to distinguish between risk associated with allopurinol starting dose and maintenance dose, that is the dose required to achieve target urate. Evidence suggests

that a higher starting dose is associated with allopurinol hypersensitivity [24], and it is unlikely that a clinical trial of sufficient power to test whether starting at lower doses reduces this risk will be undertaken. However, whether limiting the maximum allopurinol dose reduces the risk of severe reactions is less clear. This is especially important as the high-risk period is in the first weeks to months after starting allopurinol, and if dose escalation is not undertaken then individuals are potentially exposed to the risk of serious adverse events without being given the opportunity for clinical benefit if, they tolerate the drug without an adverse event on the creatinine-clearance-based dose. There is no direct evidence that limiting the dose of allopurinol in those who tolerate it reduces the risk of severe adverse reactions, and there are small studies indicating that in those who tolerate allopurinol gradual dose escalation above creatinine-clearance-based doses is not unsafe [25–27,28▪]. Given how rare these serious adverse events are, it is unlikely that any allopurinol dose escalation study will be undertaken that is sufficiently powered to detect these rare events.

The use of alternate urate lowering therapies for people with chronic kidney disease may also be problematic. Compared with allopurinol, there is more limited data on the use of febuxostat in people with gout and chronic kidney disease [29,30]. Febuxostat has also been associated with mild and severe cutaneous reactions including in those with a previous reaction to allopurinol [31,32], and some authorities have issued a warning regarding this [33]. Significantly, these reactions have been reported during postmarketing surveillance, the period in which rare adverse events are likely to be detected. Neither probenecid nor benzbromarone have been associated with severe cutaneous adverse reactions. However, probenecid is only moderately effective in those with kidney impairment [34], and while benzbromarone is effective even in those with creatinine clearance, even in those with estimated glomerular filtration rate less than 30 ml/min/1.73 m^2 [35], the risk of fatal hepatotoxicity has limited its availability [36]. As ~71% of people with gout have chronic kidney disease at least stage 2 [37], clarity around use of urate lowering therapies to achieve target urate in people with kidney disease is critical and further studies are awaited.

Role of diet and complementary therapies in the long-term management of gout

The association between diet and gout has been recognized for centuries. Dietary modification and the role of complementary therapies are particular priorities for people with gout [38], and all the current gout guidelines detail attention to diet and lifestyle. However, there is considerable variability in the information about diet available to people with gout [39]. Despite the recommendations, the evidence for an impact of dietary modification and weight loss on serum urate is poor and in many cases evidence is based on studies undertaken in people without gout. For example, in people without gout the DASH diet, which encourages intake of fruits, vegetables and low-fat dairy with reduced intake of fat and cholesterol has been recently reported to significantly lower serum urate [urate reduction −0.35 mg/dl (95% confidence interval −0.65, −0.05; $P = 0.02$)] [40]. However, the effects of dietary modification may not necessarily be the same in people with gout as seen with studies of supplemental vitamin C where a serum urate lowering has been observed in people without gout but in those with gout, the urate lowering effect was not clinically significant [41,42]. Significantly, dietary modifications are difficult to sustain long-term even with intensive patient education [43▪▪]. There is even less evidence for some of the complementary therapies such a vitamin C, cherries, turmeric and celery seed, which may people with gout use despite the expense [44,45].

Significance of asymptomatic monosodium urate crystals: are they an indication to start urate lowering therapy?

The introduction of advanced imaging techniques such as dual energy computed tomography and high resolution ultrasound has heightened awareness that in some individuals' deposition of monosodium urate crystals can occur without the associated inflammatory response which is responsible for the clinical signs and symptoms of gout. Although this may represent a 'presymptomatic' phase of disease, it is currently unknown when and what proportion of these individuals will progress to symptomatic gout, information that is critical for a risk–benefit assessment for urate lowering therapy in this setting.

Healthcare delivery to improve of long-term management of gout

Despite the differences in some aspects of current gout management guidelines, there is currently little debate that people with gout require sustained urate lowering. However, world-wide gout management remains poor with low rates of initiation and adherence with urate lowering therapy and

achieving target urate [46–48]. The majority of people with gout are managed in primary care and strategies to improve management in primary as well as secondary/tertiary settings that enhance uptake and long-term use of urate lowering therapy in a treat-to-target manner will be critical to improving gout management globally. Novel healthcare delivery strategies for people with gout including pharmacy or nurse-led management as well as the use of technology such as mobile 'apps', customized electronic medical record templates or patient portals for communication may be the way forward, and further research in these areas is required [15,49–51].

CONCLUSION

Although much progress has been made, there remain unanswered questions about many clinical aspects of gout and its management. Some of these questions may be answered by clinical trials that are currently underway or awaiting publication. For others, it may not be possible to undertake clinical trials of sufficient size and power to answer other questions. However, the interest in gout and the commitment from many world-wide to develop strategies' to improve our understanding and management of gout should give hope to healthcare providers and people with gout alike that some of these questions will be answered with time and where appropriate translate into improvements in gout management.

Acknowledgements

None.

Financial support and sponsorship

L.K.S. has received grant funds from Ardea Biosciences outside the current work.

Conflicts of interest

There are no conflicts of interest.

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