CHRONIC DISEASE MANAGEMENT 2022
https://doi.org/10.33591/sfp.48.1.u4

Unit No. 4

INITIATION OF URATE LOWERING THERAPY (ULT)

Dr Lee Meng Kam Richard, Dr Lim Yee Nah Anita

ABSTRACT

Mr Tan, 60, is a smoker with diabetes mellitus (DM), hypertension, and chronic kidney disease (CKD) Stage 3, and recurrent gout flares lasting five weeks with increasing intensity and duration. He assumes it is due to frequent travel and lack of exercise. He comes today for routine review of his chronic diseases. Current laboratory results are creatinine 106 mmol/l, eGFR 56 mL/min/1.73m², uric acid 490 µmol/L, HbA1c 7.3 percent, random hypocount 8.5 mmol/L. He is on glipizide 5 mg BD, Metformin 250 mg BD, Amlodipine 5 mg OM. He complains of severe gout pain. He had always been reluctant to start definitive treatment, which you had previously mentioned. What will you do next?

Key words: ULT, prophylaxis, colchicine, treatment targets

SFP2022; 48(1): 23-27

INDICATIONS FOR STARTING URATE LOWERING THERAPY (ULT)

ULT should be considered and discussed with every patient with a definite diagnosis of gout. ULT is indicated in patients with recurrent flare (≥2 times/year), tophi, urate arthropathy, and/or renal stones.[1]

Patients with gout should be counselled and involved in decision-making concerning the use of ULT.

ULT allows for dissolution of crystal deposits and the disappearance of gout features, provided that uric acid levels are treated to target. Effective ULT reduces the size and number of tophi and facilitates their disappearance, thereby improving quality of life, which can be seriously impaired.[2,3]

TIMING OF INITIATION OF ULT

Should urate-lowering drugs be initiated during a flare or wait until a fortnight later? Two small trials suggest that allopurinol initiation during an acute gout attack did not prolong the duration of flares nor worsen its severity as compared with delayed initiation. Early treatment in patients with comorbidities is supported by a study of a large cohort of gout patients in whom hypertension, ischaemic heart disease, and CKD were associated with increased risk of recurrence of flare.[4]

There is a need to start ULT early, particularly in patients with comorbidities and/or Serum Uric Acid (SUA) level >8 mg/dL (476 umol/L). Support to treat patients with high SUA level earlier is based on studies showing an association of hyperuricaemia with increased flare frequency.

TREATMENT TARGETS FOR ULT

For patients on ULT, the SUA level should be monitored, treated to <6 mg/dL (360 umol/L) and maintained. The exceptions are the elderly with limited life expectancy or when the patient has indicated a preference not to treat to target SUA and only for symptom control.

A lower SUA target (<5 mg/dL; 300 umol/L) is recommended for patients with tophaceous gout.

ULT should be stopped when the SUA level is <3 mg/dL (174 umol/L) as this is not recommended in the long term.

Some studies suggest that uric acid might protect against various neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis.[5,6]

HOW TO INITIATE

Types of ULT:

1. Xanthine oxidase inhibitors: XOI

- Allopurinol (1st line):

Risk factors of allopurinol-induced serious cutaneous adverse reactions (SCAR) include the presence of HLA-B* 5801 allele, starting dose of allopurinol, and renal impairment. The frequency of HLA-B* 5801 prevalence is estimated at 18.5 percent in Singapore; 1 in 5 Chinese, 1 in 15 Malays, and 1 in 25 Indians. HLA-B* 5801 genotyping is available in Singapore but is not mandatory for patients starting allopurinol. It is important to bear in mind that this test needs to be interpreted correctly. Among 100 allopurinol users with positive HLA-B* 5801, only two patients may develop serious cutaneous adverse reactions (SCAR), while among 100 patients who test negative, almost all are not at risk of developing allopurinol-induced SCAR. Therefore,

DR LEE MENG KAM RICHARD
Senior Consultant
National Healthcare Group Polyclinics

DR LIM YEE NAH ANITA
Senior Consultant
Division of Rheumatology
National University Hospital

the test may deny many people who will not have developed SCAR from allopurinol, a cheap and effective means to lower uric acid.

Allopurinol should be started at a low dose (100 mg/day) even in patients with normal kidney function to reduce the likelihood of an early gout flare. A high starting dose increases the risk of SCAR.[7,8] An optimal dose of allopurinol 300 mg/day achieves the SUA target of 6 mg/dL (360 umol/L) in about 70-80 percent of patients.

Treatment with allopurinol can be titrated up to 600-800 mg/day. Compliance must be ascertained prior to escalating doses.

Allopurinol may be combined with a uricosuric agent if target SUA cannot be attained in the presence of continued flares. Febuxostat or a uricosuric agent is indicated if allopurinol cannot be tolerated.

In patients with renal impairment, allopurinol should start low at 50 mg OM. Titration of the dose should be much slower to achieve and maintain the same target SUA as in patients with normal renal function.

Renal failure is associated with an increased risk of SCARs and poor outcome. Decreased renal function results in decreased clearance and higher serum levels of oxypurinol, which can induce a cytotoxic T-cell response and trigger hypersensitivity reactions in SCARs.

HLA-B*5801 genotype testing does not prevent SCAR events in high-risk patients. All prescribers are reminded that close monitoring of patients (4-6 weeks) post-initiation of allopurinol is prudent. When starting allopurinol, patients should be cautioned that, should they develop a rash, they should seek prompt medical attention and stop allopurinol immediately.

- Febuxostat:

Febuxostat is a potent non-purine selective xanthine oxidase inhibitor, which is metabolised in the liver and not excreted via the kidneys. Therefore, it can be considered for use in patients with allopurinol allergy or moderate to severe renal impairment. The normal daily dose of febuxostat is 80 mg.

Febuxostat has been found to be more effective in patients with CKD than allopurinol given at doses adjusted to creatinine clearance. Febuxostat should be avoided in or used with particular caution in patients with high cardiovascular risk.

2. Uricosuric agents

- Probenecid (1-2 g/day) – Do not use in patients with renal stones or renal impairment (Creatinine clearance < 30ml/min).

- Benzbromarone (50-200 mg/day) – this is not commonly used in the primary care setting.

A review for side effects is recommended after 4-6 weeks with slow upward titration of ULT in every patient.

Prophylaxis with colchicine is recommended during the first six months of ULT.

Recommended prophylaxis is colchicine, 0.5-1 mg/day, in which the dose should be reduced in patients with renal impairment. Clinicians should be aware of potential neurotoxicity and/or muscular toxicity with prophylactic colchicine in renal impairment or statin treatment. Co-prescription of colchicine with strong P-glycoprotein and/or CYP3A4 inhibitors should be avoided. If colchicine is not tolerated or is contraindicated, low dose prednisolone may be used but caution is needed in diabetics. Occasionally, as needed NSAIDs may be sufficient.

REVIEW OF PATIENT AFTER 4-6 WEEKS

Side effects from medications and breakthrough gout flares should be monitored with full blood count (FBC), uric acid, alanine aminotransferase (ALT), and creatinine level (Table 1). The patient can be counselled by a dietitian and nurse manager on lifestyle and diet.

Table 1: Side Effects of Allopurinol

Side effects	Warning signs	Things you need to do
Allergic reaction, especially skin reactions (if it occurs, it usually does so within the first few weeks to three months).	Skin rashes, itching, redness, burning sensation. Fever, sore throat, red eyes, or mouth sores may be early symptoms	Stop medication and see a doctor immediately as this may be a serious allergy. If the rash is mild, your doctor may re-introduce Allopurinol at a lower dose at another time.
Reduced blood counts (rare)	There may be no warning signs but unusual bleeding or bruising, lip or mouth ulcers with flu-like symptoms may occur	Inform your doctor immediately if these symptoms occur. Go for regular blood tests.
Liver abnormalities	Usually none, jaundice may occur	Go for regular blood tests.
Nausea, loss of appetite, or diarrhoea		Take medication after food or divide the dose into two to be taken within the day

Clearly document counselling and monitoring for side effects.

1. Instruct ACTION PLAN if patient develops any of the above:
   - Stop Allopurinol immediately. DO NOT take the next dose.
   - Stop taking medications (there is no need for permission from doctors).
   - Seek medical attention (A&E) and inform any doctor of new drug, allopurinol (even if it was started in the past 3-4 months).
2. Explain the SEVERITY (What happens if drug is not stopped in time):
   - Allergic reaction can affect internal organs like the liver and kidneys, and if the reaction is severe, death can occur.
3. End counselling on a reassuring note that you are accessible
   - Call the clinic if those symptoms occur, and inform the patient that you will provide close monitoring.

Common FAQs:

1. **What if I miss a dose?**
   If you miss a dose or forget to take your medicine, take it as soon as you remember it.

   If it is almost time for your next dose, skip the missed dose and continue with your regular schedule. Do not double the dosage to make up for the missed dose.
2. **Should I continue or stop taking Allopurinol during an acute gout attack?**
   If you have been taking Allopurinol regularly, you should continue taking it during an acute gout attack, along with other medications to treat the acute gout attack.
3. **Cain I drink alcohol while taking Allopurinol?**
   Avoid or limit alcohol intake while on this medicine as alcohol can increase the amount of uric acid in your blood. Alcohol consumption can trigger acute gout attacks.
4. **Are there any medications to avoid while on Allopurinol?**
   Allopurinol may increase the effects of warfarin, Azathioprine, and Mercarptopurine, and may increase the incidence of skin rashes in patients taking Ampicillin.

ACUTE TREATMENT FOR GOUT FLARES

An acute gout flare is an intensely painful and disabling inflammatory arthritis, usually involving a single joint, but occasionally involving two or more joints (Table 2).

Acute flares should be treated as early as possible. Fully informed patients can be taught to self-medicate at the first warning symptoms.

Choose drug(s) based on contraindications, the patient's previous experience with treatments, time of initiation after flare onset, and the number and type of joint(s) involved.

Table 2: Gout Classification Criteria

Criteria (2015 ACR-EULAR)[9]		**Categories** ***Please select the highest category ever noted for each criterion.***
CLINICAL	Pattern of joint/bursa involvement during symptomatic episode(s) ever	Joint(s) *or* bursa(e) other than ankle, midfoot or 1st MTP (or their involvement only as part of a polyarticular presentation)
		Ankle *or* midfoot (as part of monoarticular or oligoarticular episode without 1st MTP involvement)
		MTP (as part of monoarticular or oligoarticular episode)
	Characteristics of symptomatic episode(s) ever: (i) Erythema overlying affected joint (patient-reported or physician-observed) (ii) Can't bear touch or pressure to affected joint (iii) Great difficulty with walking or inability to use affected joint	No characteristics
		One characteristic
		Two characteristics
		Three characteristics

	Time-course of episode(s) ever: Presence (ever), irrespective of anti-inflammatory treatment: (i) Time to maximal pain <24 h (ii) Resolution of symptoms in ≤14 days (iii) Complete resolution (to baseline level) between symptomatic episodes	No typical episodes
		One typical episode
		Recurrent typical episodes
	Clinical evidence of tophus: Draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity, located in typical locations: joints, ears, olecranon bursae, finger pads, tendons (e.g., Achilles)	Absent
		Present

Recommended therapeutic options for acute flare include:

1. Colchicine
2. NSAIDs
3. Corticosteroids

Colchicine

Colchicine may be used (within 12 hours of flare onset) at a loading dose of 1 mg followed by 0.5 mg an hour later on day 1 and/or colchicine tablets of 0.5 mg BD/TDS.

Use colchicine with caution in patients with severe renal or liver impairment.

Drug interactions between colchicine and strong P-glycoprotein and/or CYP3A4 inhibitors such as cyclosporin or clarithromycin and simvastatin may mean that it is safer to avoid colchicine.

In patients with frequent flares and contraindications to colchicine, use NSAIDs or corticosteroid (oral and injectable).

Combination therapy, such as colchicine and NSAID or colchicine and corticosteroids, can be prescribed for patients with particularly severe acute gout.

IL-1 blockers are prohibitively expensive and rarely used for treating prolonged refractory flares in the tertiary care setting. Acute infection is a contraindication to their use.

COX1 and COX2 inhibitors

Avoid using in patients with renal impairment CKD 3 and active peptic ulcer disease.

Caution is needed in patients with known cardiovascular disease as an increased risk of myocardial infarction, stroke, and heart failure has been associated with these drugs, although whether such risk is increased in patients receiving short courses of NSAID for a gout flare is unknown.

There is no preference of one particular NSAID over others. Common NSAIDs (COX-1), indomethacin 50 mg TDS, naproxen 550 mg BD, and diclofenac sodium 50 mg TDS or (COX-2) Etoricoxib 90 or 120 mg OM (maximally for a week) can be used.

The total duration of NSAID therapy for a gout flare is five to seven days.

Corticosteroids

Oral corticosteroids may be used, especially in patients with renal impairment or drug allergies. Use prednisolone 30-35 mg/day for 3-5 days.

GENERAL ADVICE

1. Adequate hydration and rest
2. Removal of medication triggers, e.g., diuretics
3. Avoid high purine foods, sugar sweetened drinks, and alcohol (beer)
4. Apply ice packs

REFERENCES

1. Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castañeda-Sanabria J, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis. 2017 Jan;76(1):29-42. doi: 10.1136/annrheumdis-2016-209707. Epub 2016 Jul 25. PMID: 27457514.
2. Neogi T, Jansen TL, Dalbeth N, Fransen J, Schumacher HR, Berendsen D, et al. 2015 Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2015 Oct;74(10):1789-98. doi: 10.1136/annrheumdis-2015-208237. Erratum in: Ann Rheum Dis. 2016 Feb;75(2):473. PMID: 26359487; PMCID: PMC4602275.
3. Teng GG, Ang LW, Saag KG, Yu MC, Yuan JM, Koh WP. Mortality due to coronary heart disease and kidney disease among middle-aged and elderly men and women with gout in the Singapore Chinese Health Study. Ann Rheum Dis. 2012 Jun;71(6):924-8. doi: 10.1136/ard.2011.200523. Epub 2011 Dec 15. PMID: 22172492; PMCID: PMC3400339.

4. Pascual E, Sivera F. Time required for disappearance of urate crystals from synovial fluid after successful hypouricaemic treatment relates to the duration of gout. Ann Rheum Dis. 2007 Aug;66(8):1056-8. doi: 10.1136/ard.2006.060368. Epub 2007 Jan 12. PMID: 17223663; PMCID: PMC1954685.
5. Paganoni S, Schwarzschild MA. Urate as a Marker of Risk and Progression of Neurodegenerative Disease. Neurotherapeutics. 2017 Jan;14(1):148-153. doi: 10.1007/s13311-016-0497-4. PMID: 27995438; PMCID: PMC5233635.
6. Cutler RG, Camandola S, Malott KF, Edelhauser MA, Mattson MP. The Role of Uric Acid and Methyl Derivatives in the Prevention of Age-Related Neurodegenerative Disorders. Curr Top Med Chem. 2015;15(21):2233-8. doi: 10.2174/1568026615666150610143234. PMID: 26059354; PMCID: PMC5851449.
7. Perez-Ruiz F, Lioté F. Lowering serum uric acid levels: what is the optimal target for improving clinical outcomes in gout? Arthritis Rheum. 2007 Oct 15;57(7):1324-8. doi: 10.1002/art.23007. PMID: 17907217.
8. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken). 2012 Oct;64(10):1431-46. doi: 10.1002/acr.21772. PMID: 23024028; PMCID: PMC3683400.
9. Khanna D, Khanna PP, Fitzgerald JD, Singh MK, Bae S, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and anti-inflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res (Hoboken). 2012 Oct;64(10):1447-61. doi: 10.1002/acr.21773. PMID: 23024029; PMCID: PMC3662546.

LEARNING POINTS

- **ULT is indicated in patients with recurrent flare >2 times per year, tophi, urate arthropathy, and/or presence of renal stones.**
- **While different xanthine oxidase inhibitors and uricosuric agents can be used, the indication for starting medication, action plan, and side effects must be explained to the patient.**
- **Prophylaxis (colchicine or low dose oral corticosteroids for those who cannot take colchicine) should be commenced during the early months of ULT to reduce the risk of additional flares, which are common early in the course of ULT. Allopurinol should be continued during acute attacks for patients already on this.**