
بسم الله الرحمن الرحيم

Gout Treatment

M.Akhlaghi
Associate Professor of Rheumatology
Rheumatology Research Center
Tehran University of Medical Sciences

Education & lifestyle

- Independent associations for increasing risk of gout: adiposity, weight gain, hypertension and diuretic use
- Protective factor: weight loss & control weight
- Dietary risk factors for gout: meat, seafood, beer
- Potential protective effect: dairy products
- Smoking cessation
- Stay well hydrated

Diet

- Coffee: Drinking a moderate amount of coffee a day can lower gout risk.
- Fructose: Consumption of sugar-sweetened soft drinks and fructose was strongly associated with an increased risk of gout.
- Vitamin C: The potential mechanisms by which vitamin C reduces serum urate levels include competition for its renal reabsorption and increased glomerular filtration of urate (uricosuric effect).
- Antioxidant-rich fruits: Dark-colored fruits like blackberries, blueberries, raspberries, grapes and especially cherries can help keep uric acid under control.

Diet

- Avoid: Organ meat
  High fructose corn syrup–sweetened drinks
  Alcohol overuse
- Limit: Beef, lamb, shellfish, Beer

- Encourage: Low-fat dairy

Comorbidity & potential complications

- Metabolic syndrome: Atherosclerotic risk factors, with abdominal obesity and insulin resistance being the predominant underlying components. Other metabolic components include atherogenic dyslipidemia, elevated blood pressure, and elevated plasma glucose.

- Cardiovascular disease and mortality: epidemiological studies suggest an independent association between increasing urate levels and the risk for CVD.

Comorbidity & potential complications

- Type 2 diabetes: Expanding on the strong associations between hyperuricemia, gout, and the metabolic syndrome, preliminary data showed that male participants with gout had a 41% increased risk for incident type 2 diabetes
- Also increasing serum urate levels were associated with an increased risk of type 2 diabetes.

Medication

- Acute Gout
- Prophylaxis of Acute Gout
- Medications for Prevention of Chronic Gout

Acute Gout

- NSAIDS
- Colchicine
- Corticosteroids

Acute Gout

- Issues critical to treatment success for a gouty flare are the early initiation of treatment, ensuring adequate dosing of anti-inflammatory therapy, and continuing the treatment until the flare has completely resolved (usually 6 to 10 days). During the acute flare, subjects already taking urate-lowering therapy should continue the drug, whereas those not receiving this therapy should not be started.

Prophylaxis of Acute Gout

- NSAIDS
- Colchicine

Anti-inflammatory prophylaxis should be continued until the subject has been free of gout flares for 6 months or longer.

Prevention of Chronic Gout

- Colchicine
- Pegloticase
- Urate-Lowering Therapy:

❖Xanthine Oxidase Inhibitors (XOIs):

Allopurinol, Febuxostat

❖Uricosurics:

Probenecid, Sulfinpyrazone, Benzbromarone, Lesinurad

Allopurinol

- The ACR guidelines recommend that the allopurinol starting dose be no greater than 100 mg/day. The dose is gradually escalated by 100 mg daily every 2 to 5 weeks, with serum urate monitoring until the target serum urate is achieved. The maximal U.S. FDA-approved dose of allopurinol is 800 mg daily. In subjects with advanced chronic kidney disease, the initial dose should be reduced to 50 mg daily, with incremental dose escalations of 50 mg.

Allopurinol

- About 80% of allopurinol is excreted in the urine, most of it in the form of oxypurinol , which accumulates in patients with chronic kidney disease, this seems to predispose to severe cutaneous adverse reactions (SCARs) and led to recommend limitation of allopurinol dosage in CKD patients.
- SCARs to allopurinol usually occur, as most of the benign reaction to the drug, in the first 3 months of treatment. Mortality rate is 10-30%. The incidence of Toxic Epidermal Necrosis/Stevense Johnson syndrome has been estimated in the USA at 0.69 per 1000 allopurinol initiators and appears to be greater in Blacks and Asians and particularly Chinese (association with HLA*B5801).

Feboxostat

- Feboxostat: xanthine oxidase inhibitor that was approved by the FDA in 2009. Although feboxostat is superior to 300 mg allopurinol at lowering serum uric acid levels, it is not more effective at reducing the frequency of gout flares, and it is conciderably more expensive than allopurinol.

- The ACR gout management guidelines recommend either allopurinol or feboxostat as first-line ULT and the EULAR guidelines recommend feboxostat as a second-line therapy for patients that do not tolerate allopurinol.

Feboxostat

- No dose adjustment of feboxostat is necessary for elderly patients or for patients with mild to moderate renal impairment (creatinine clearance 30-89 ml/min) or mild to moderate liver impairment (Child-Pugh class A or B).
- In patients with creatinine clearance below 30 ml/min, feboxostat is not approved.
- Feboxostat is not a purine, uricosurics have no effect on its plasma concentration, and feboxostat-uricosuric combination is believed to be particularly effective.

Feboxostat

- Concerns about the cardiovascular safety of febuxostat arose from the APEX and FACT trials, in which a numerically greater incidence of investigator-reported cardiovascular events was observed under febuxostat, as compared with allopurinol. However, no definite conclusion could be drawn as the observed differences were not statistically significant.

Feboxostat

- CARES study is a multicenter, double-blind, noninferiority trial that involved 6190 patients with gout and major cardiovascular disease, randomly assigned to allopurinol or febuxostat after stratification by renal function. Both drugs were titrated to reach the less than 6 mg/dl serum uric acid (SUA) target, which was obtained in a similar proportion (69–75%) in the two groups along the trial duration. Patients were followed up for a median of 32 months.

Feboxostat

- In CARES study significantly more cardiovascular deaths occurred in the febuxostat group (4.3%) as compared with the allopurinol group (3.2%) (P=0.03), and all-cause mortality was significantly more frequent in the febuxostat group (7.8 versus 6.4%, P=0.04).

Feboxostat

- Comparative effectiveness of urate lowering with feboxostat versus allopurinol in gout: analyses from large U.S. managed care cohort

- This retrospective study utilized 2009 to 2012 medical and pharmacy claims and laboratory data from a large U.S. commercial and Medicare Advantage health plan.

- Singh et al. Arthritis Research & Therapy (2015) 17:120 DOI 10.1186/s13075-015-0624-3

Feboxostat

- In this study that at the currently used doses, febuxostat (most common dose of 40 mg/day) was more effective in achieving the target sUA than allopurinol (most common doses of 300 mg/day or lower). The time to achieve target sUA in the febuxostat group is a month shorter than in the group receiving allopurinol. Slight improvements in renal function were noted with both allopurinol and febuxostat.

- Singh et al. Arthritis Research & Therapy (2015) 17:120 DOI 10.1186/s13075-015-0624-3

Uricosurics

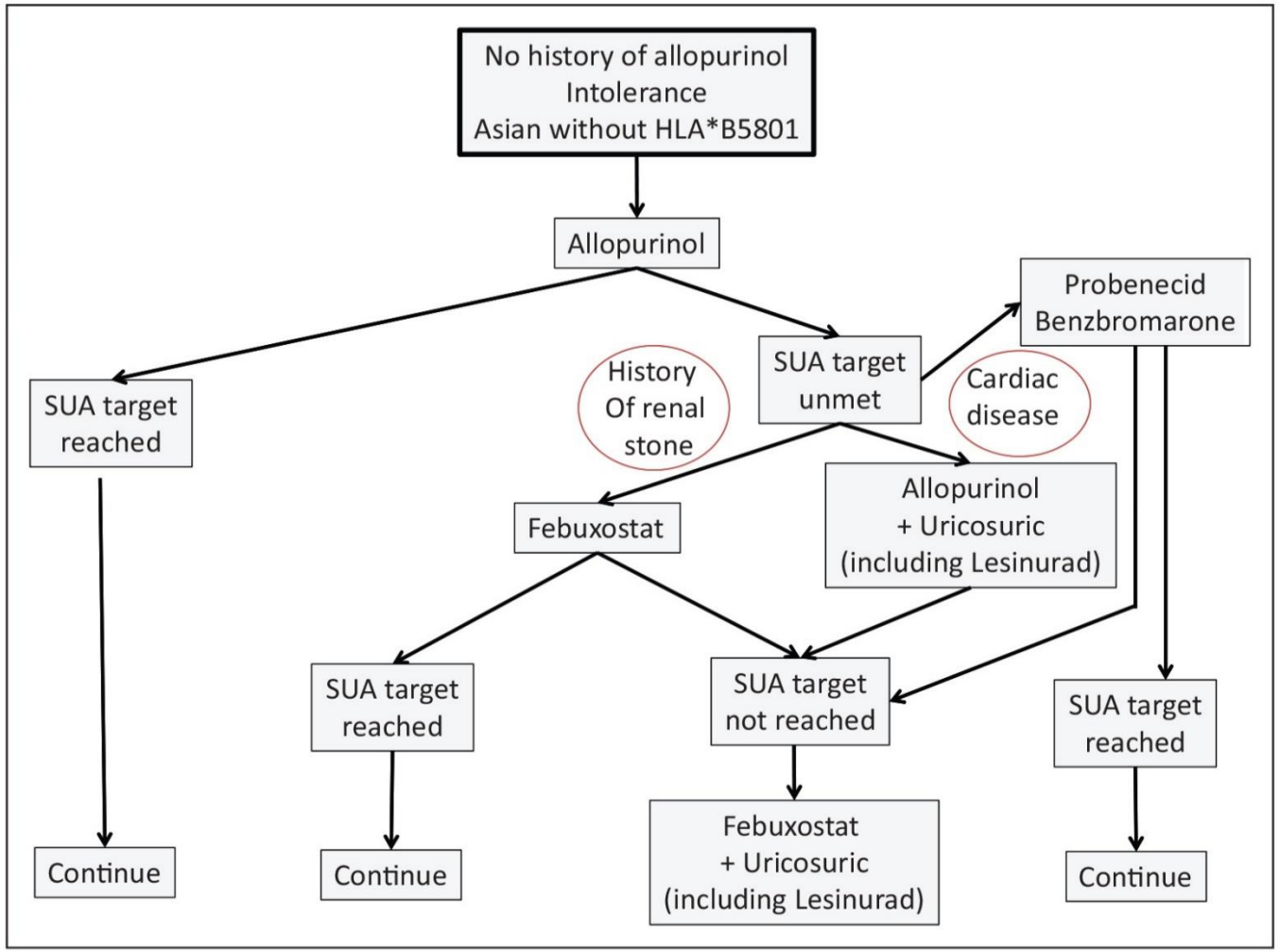
- Uricosurics are contraindicated in patients with a history of kidney stone, when used alone.
- Probenecid
- benzbromarone
- Sulfinpyrazone
- Lesinurad

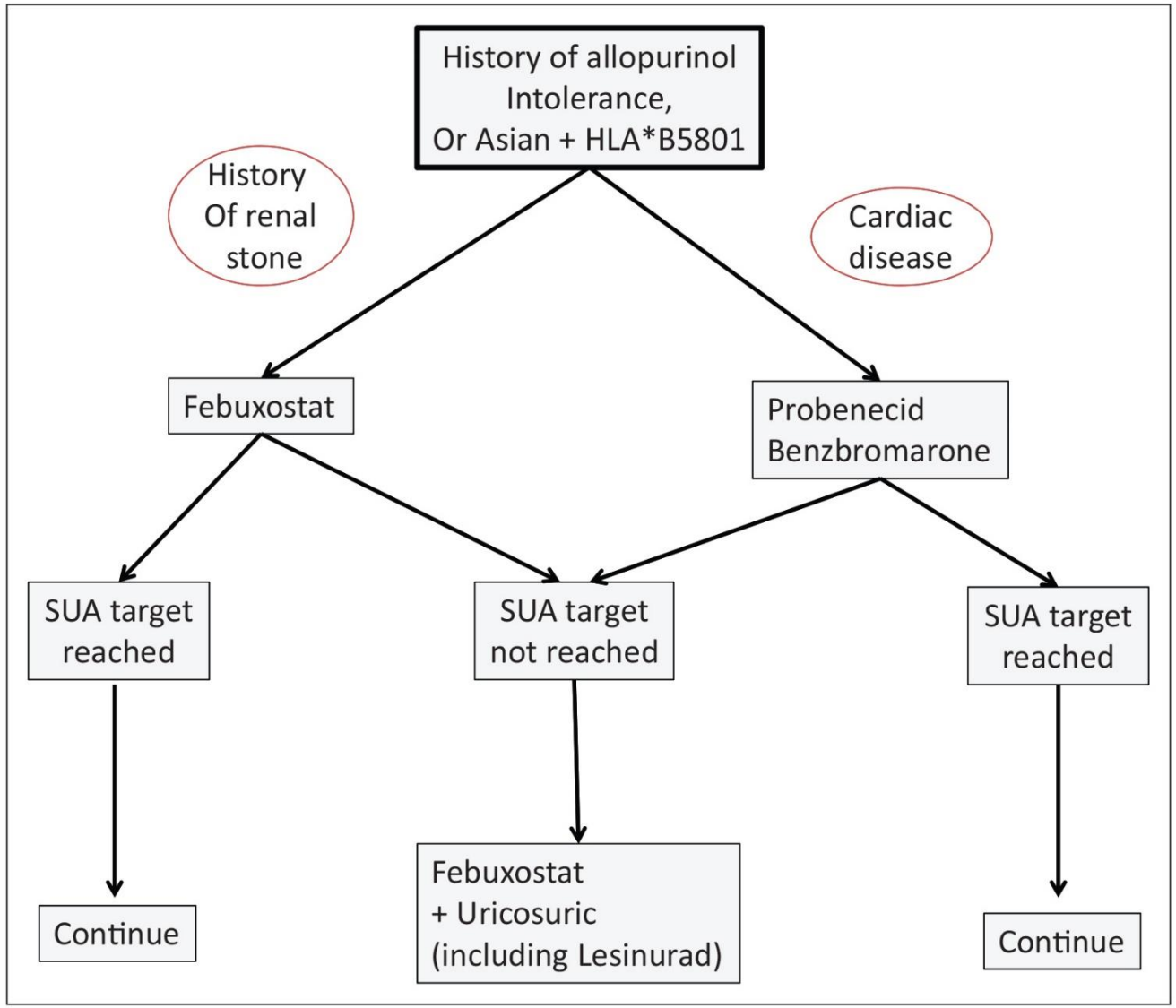
Lesinurad

- Lesinurad exerts its effect on reducing SUA by inhibiting the reabsorption of filtered urate
- Lesinurad is licenced at a daily dose of 200mg in combination with a XOI for the treatment of hyperuricemia in those with gout in the USA and Europe, if the former cannot achieve target SUA on its own.

Lesinurad

- Lesinurad is not approved for the treatment of asymptomatic hyperuricaemia, or for use without a XOI. In published studies, it was taken in the morning,with food and a cup of water and the participants were required to maintain at least 2-l fluid intake/day.
- Renal toxicity remains one of the main concerns for lesinurad, especially those treated with this drug alone.


No history of allopurinol Intolerance Asian without HLA*B5801
Allopurinol
SUA target reached
Continue
SUA target unmet
History Of renal stone
Cardiac disease
Probenecid Benzbromarone
Febuxostat
Allopurinol + Uricosuric (including Lesinurad)
SUA target reached
Continue
SUA target not reached
Febuxostat + Uricosuric (including Lesinurad)
SUA target reached
Continue


History of allopurinol Intolerance, Or Asian + HLA*B5801
History Of renal stone
Cardiac disease
Febuxostat
Probenecid Benzbromarone
SUA target reached
SUA target not reached
SUA target reached
Continue
Febuxostat + Uricosuric (including Lesinurad)
Continue

Pegloticase

- Pegloticase is an intravenous uricase approved by the FDA in 2010. The mechanism of action involves metabolism of uric acid to allantoin.
- It is a third-line agent and is indicated for treatment of refractory gout. It is usually administered every two weeks at a cost of more than 5000 dollers per dose.

Refractory Gout

- Feboxostat
- Feboxostat+Uricosuric
- Feboxostat+Lesinurad
- Pegloticase

Conclusion

- XOIs remain first line for the management of hyperuricaemia in people with gout. The indications for lesinurad in real-world clinical scenarios may include inability to achieve target SUA levels despite maximum licenced doses of XOI, or inability to tolerate sufficiently high doses of a XOI that allows reduction in SUA to below the treatment target level. Lesinurad should be preferred over other uricosuric drugs such as sulfinpyrazone and probenecid given the potential for side effects and drug interactions with these medicines.

Conclusion

- Despite the recent licencing of lesinurad, there is still need for a urate-lowering agent that can be used in the presence of significant renal impairment.

Conclusion

- Febuxostat remains a useful addition to the ULDs available for the management of gout and decreased the number of patients refractory to oral urate-lowering treatment. However, recent reinforcement of concerns about the cardiovascular tolerance leads to restriction in its role in the management of gout.

References

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Thanks For Your Attention
JORDAN ROBINS