Gout 2019 - is an old disease finally coming of age, or not

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Gout and its place in world history

Gout and its place in ancient history

“Persons affected with the gout who are aged, have tophi in their joints, who have led a hard life, and whose bowels are constipated are beyond the power of medicine to cure” — Hippocrates c. 400 BCE

James Gillray: 18th Century

Gout and its place in prehistory

Pity a Tyrannosaur? Sue Had Gout
By Malcolm W. Browne

For all the suffering she probably caused her Cretaceous prey, a tyrannosaur named Sue seems to have paid dearly. Scientists have determined that the big dinosaur probably was a victim of agonizing gout and other debilitating ailments.

James Gillray: 18th Century
Why give update on gout at Advances in Internal Medicine?

1. Gout is prevalent: 2007-2008 NHANES 3.9% (8.3 million)\(^3\)
   - Men = 5.9% (6.1 million)\(^1\)
   - Women = 2.0% (2.2 million)\(^1\)
   - Prevalence has increased by 1.2 percentage points (30%) in past two decades\(^2\)
   - Crystalline arthritis accounted for 2.3% (39 million) admissions\(^2\)
   - Gout responsible for 5% (5 million) outpatient visits 2010\(^2\)

2. Gout is treated primarily by PCP’s in U.S.
   - Only 1.3 % of all outpatient visits for gout treated by rheumatologists\(^1\)
   - 70% of patients with gout are under the care of primary care physicians
   - Only 3% of gout patients are referred by PCP’s to rheumatologists

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3 Only 1.3 % of all outpatient visits for gout treated by rheumatologists\(^1\)
Why give update on gout at Advances in Internal Medicine?

3. Gout is generally mismanaged
   • Underuse of uric acid lowering therapy (ULT) in eligible patients likely to benefit
   • Under-dosing of allopurinol in patients on ULT (40% with serum uric acid >6 on current dose)
   • Initial overdosing of allopurinol in some patients at risk for hypersensitivity

4. Plethora of urate lowering therapies currently available or coming to market

Gout in recent general medical literature

ACP Guidelines 2017: Extraordinary disappointment
Gout guidelines published by rheumatology societies

Acute Gout

- Acute, usually self limited monoarticular inflammatory arthropathy
- Inflammatory response directed against monosodium urate crystals in synovium
- Usually but not always associated with hyperuricemia
- Monosodium urate crystals precipitate around at a concentration of 6.8 mg/dL, within reference range in most US populations

Distribution of Serum Uric Acid Levels in Japan: 34,000 People
Acute Gout Diagnosis
- **Definitive:** Crystal identification – the only way!
  - Joint fluid examination under polarized microscopy with red compensator
  - Strongly negatively birefringent needle shaped crystals
- **Suspected:** Characteristic radiographic “gouty” corticated erosions away from joint space
- **Possible:** Classic clinical picture with elevated serum urate
- **However:** Presence of hyperuricemia alone is not diagnostic of gout

Therapy for Acute Gouty Flares
- Acute gout attacks are often self limited (3-5 days)
- Goals: Reduce both severity and duration of attack
- **NSAIDs**
  - Effective and rapid relief of symptoms
  - Contraindicated in patients with GI, Renal, or hypersensitivity concerns
- **Corticosteroids** (intra-articular and/or systemic [0.5 mg/kg/day followed by modest taper])
  - **Colchicine:**
    - Low dose only (0.5 mg BID) Not every hour until patient gets sick
    - Must be used within 48 hours of attack onset (blocks leukocyte migration)
    - Likely not as effective as either NSAIDs or corticosteroids

Colchicine: How Effective for Acute Gout??

<table>
<thead>
<tr>
<th>Therapy</th>
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<th>Mayo score</th>
<th>VAS</th>
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<tr>
<td>Placebo</td>
<td>1.0-1.5 mg/day</td>
<td>13.0/45</td>
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Fewer than 40% of patients achieve primary endpoint
High dose no more efficacious and more toxic
55 year old male with a history of known gout awakens with right knee pain and swelling one morning that worsens over next 48 hours until he has difficulty walking on that knee. On a recent Chem. 20 panel, uric acid level was elevated at 10.7. He denies any other joint pains, IVDU, or recent sexual contacts. After undergoing arthrocentesis confirming the diagnosis of gout and ruling out an infectious process, the patient is started on indomethacin and allopurinol 300 mg/day and sent home. Which of the following actions in this case was a mistake?

- A. Allopurinol dose
- B. Indomethacin therapy
- C. The patient was not admitted and treated with antibiotics until synovial fluid cultures were negative for 5 days
- D. Use of allopurinol during acute phase of gout

Chronic Gout - Progression

- More frequent inflammatory arthritic attacks
- Monoarticular attacks
- Same joint
- Spread to other joints
- Polyparticular attacks of arthritis as disease progresses
- Attacks blend together/ No longer completely self-limited
- Chronic synovitis resembling rheumatoid arthritis
- Destructive arthritis/Tophaceous gout:
  - Uric acid containing tophi deposit in joints/tendons/soft tissues, can lead to erosions and deformities

Chronic Gout – 2012 ACR guidelines

- Goal: Treat to target uric acid level
  - Lower serum uric acid levels are associated with fewer attacks
  - Target serum uric acid level below crystallization concentration (< 6.0 or even 5.0 in severe gout) to reabsorb tophi and remove UA stores
  - 1st line Uric acid lowering therapies: allopurinol and Febuxostat
  - Other therapies now available to get uric acid levels to target for patients who fail or are contraindicated/intolerant to 1st line meds

- Prophylaxis
  - Prophylaxis against acute gout flares at least 3 months when initiating or adjusting uric acid lowering therapy (Europeans recommend six months)
  - Colchicine does work well for this (0.6 mg/day usually suffices)
  - NSAIDs and prednisone work as well
Treating hyperuricemia: ACR 2012 guidelines

- Do not treat asymptomatic hyperuricemia
  - Primary hyperuricemia may someday be linked to cardiovascular or metabolic syndromes
- General goal is:
  - To reduce frequency and severity of subsequent attacks of gout
  - To resorb tophaceous uric acid deposits that can cause joint damage
- Allopurinol and febuxostat are considered first-line therapies for hyperuricemia associated with gout

ACP Guidelines: Key failure

- The ACP expert panel couldn’t bring itself to recommend treating to a serum uric acid target
- Cited lack of evidence to recommendation (formal randomized prospective trials comparing treating to specific target on outcomes of gout flares, tophus reduction, metabolic syndrome, etc...)
- Cited clinical trials of urate lowering therapy with increased gout flares (lacked adequate prophylaxis)
- Ignored its own cited mountains of other literature/evidence (2 RCTs post-hoc analysis and 8 retrospective cohort studies) supporting long term reduction in gout flares and complications of hyperuricemia with treatment to serum urate <6 and better if < 5.
- Ignored common sense: “The guideline..... imperils good outcomes, and could set optimal treatment of the disease back decades.” – R. Turkeltaub MD UCSD

Addressing co-morbid conditions in gout patients with hyperuricemia

- Patient education about hyperuricemia, diet, and lifestyle modifications
- Consideration given to uric acid-elevating medications
- Key culprits are thiazide and loop diuretics, niacin, and cyclosporine
- Obviously if drug benefits outweigh small improvement in uric acid, then do not adjust or discontinue
Question 2

A 62 YO male patient of yours with gout comes to your office asking what dietary changes he should make in helping to treat his gout and hyperuricemia. According to the ACR guidelines, you recommend that he avoid which of the following?

A. Modest alcohol intake
B. Foods and beverages with high fructose corn syrup
C. Chicken and turkey
D. Low fat dairy products

Diet recommendations:
Fairly Meager evidence

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<tr>
<th>Food</th>
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</thead>
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<td>High fructose corn syrup</td>
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<td>b</td>
</tr>
<tr>
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Chronic Gout: Uric Acid Lowering Therapies

- Allopurinol
  - Xanthine Oxidase Inhibitor (blocks metabolism of purines to uric acid)
  - Effective for both under-excreters and overproducers of uric acid
  - Now acceptable to start many gout patients on allopurinol during a flare if they are responding appropriately to anti-inflammatory agents
  - Don’t stop therapy during an acute attack
Allopurinol is a purine derivative: a dead ringer for hypoxanthine. Allopurinol competes with hypoxanthine for xanthine oxidase.

Using allopurinol properly:

- Do not start patients on more than 100 mg/day.
- Dose reduce ALL patients with moderate to severe renal insufficiency.
- Gradually up-titrate the dose, which in some cases, can be more than 300 mg/day if needed.
- Treat to Target: serum urate concentration <6 if treating tophi, and <5 ideally.
- Push the allopurinol dose over 300 mg/day if necessary!!

EULAR 2016 Treat to Target Recommendations
Allopurinol Toxicities

- Careful use in patients with renal failure
  - Metabolites are renally cleared
- Hypersensitivity reactions are more common in patients with renal insufficiency
- Purine-associated hypersensitivity syndrome is DIFFERENT from allergic rash: Systemic and sometimes life threatening illness
  - Fever, Steven's Johnson/TEN, hepatitis, marrow suppression, nephritis, DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) The Role of HLA 5801 and Allopurinol Hypersensitivity is unquestioned
  - All patients from populations with a high allele frequency for HLA 5801 and high hazard ratio for developing hypersensitivity should be screened!!

Allopurinol Pharmacogenetics

1. The Role of HLA 5801 and Allopurinol Hypersensitivity is unquestioned
2. All patients from populations with a high allele frequency for HLA 5801 and high hazard ratio for developing hypersensitivity should be screened!!

HLA BS801 and Allopurinol Hypersensitivity
Hung et al. PNAS 2005

<table>
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<tr>
<th>Allele</th>
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1. BS801 confers nearly 600 fold increased risk of allopurinol hypersensitivity
2. Allele and association is particularly important in Han Chinese patients, Thai, and Korean patients.

The Present State of Gout Therapy: What to do with a More Challenging Case?

You are seeing a 56 year old male with long standing diabetes, hypertension, chronic renal insufficiency, and destructive tophaceous gout. His gout originally began as episodic podagra that became more frequent and involved more joints over time. In the past few years, his tophi have grown larger and more numerous, and acute episodes of inflammatory arthritis have begun to blend together into a chronic, painful, polyarticular inflammatory synovitis in his hands, elbows, knees, and feet from which he has come to your office seeking relief.
Gout: Findings

- He has chronic swelling, synovitis, and deformities reminiscent of rheumatoid arthritis
- Numerous tophi scattered on arms, legs, and ears
- Serum creatinine is 1.8
- Uric Acid 10.2

Managing the Chronic Disease

Which of the following options is best suited to treat his hyperuricemia to target:

A. Starting allopurinol 300/day
B. Colchicine 0.6 mg/day
C. Probenecid 250 mg twice daily
D. Start febuxostat 40 mg/day

Managing the Chronic Disease

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Difficult to manage chronic gout

- Generally do not start 300 mg/day of allopurinol on most patients, especially with chronic kidney disease
- Mechanism of colchicine doesn’t treat hyperuricemia
- Probenecid won’t work without adequate GFR and is contraindicated in tophaceous gout anyway
- Starting very low allopurinol (50mg or 100 mg QOD and titrating up is an option, but febuxostat is effective and safe in patients with moderate CKD
Febuxostat (FDA approved 2009)
- First treatment in 40 years for chronic gout
- NON-PURINE inhibitor of xanthine oxidase
- Theoretically safe to use in patients with allopurinol reactions
- Been studied in patients with mild renal insufficiency
- Dosed at 40-80mg/once daily

Fubuxostat is Not a Purine

Purine Metabolism

Comparison of Febuxostat to Allopurinol
Becker et al. NEJM 2005
- 80mg and 120 mg of febuxostat superior to allopurinol 300mg/day
- Percent of patients achieving uric acid levels
- Greater reductions in serum uric acid levels
- Safe in patients with mild-moderate renal insufficiency (SCr < 1.5 in this study) and patients with previous allopurinol reactions
- Note: Allopurinol 300/day is probably suboptimal dose for many patients
CARES Trial design

- Randomized double-blind non-inferiority trial of effect of allopurinol vs. febuxostat on CV events in gout patients with uric acid >7 and previous history of CV
  - CV defined as MI, unstable angina or TIA hospitalization, CVA, hx. revascularization procedure, peripheral vascular disease, or diabetes with microvascular disease
  - Events defined as non-fatal MI or CVA, unstable angina needing revascularization, or CV death.
  - Modified intention to treat analysis with non-inferiority set at HR<1.3
  - Randomization stratified according to baseline creatinine clearance

CARES Protocol

- Patients randomized to allopurinol started between 100-300 mg/day depending upon creatinine clearance
- Titrated up to a max of either 400 mg or 600 mg/day depending upon renal function if target uric acid was >6.
- Febuxostat treated patients started 40 mg/day and were titrated up to 80 mg/day if target uric acid > 6

CARES Results

- 6190 patients randomized
- Median 32 month follow up
- 57% discontinued treatment and 45% lost to follow up
- Primary end point occurred in 10.8% febuxostat and 10.4% allopurinol groups (HR 1.03)
Results: Major safety end points

<table>
<thead>
<tr>
<th>Event</th>
<th>Febuxostat</th>
<th>Allopurinol</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major safety outcomes (defined as cumulative incidence)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality: death due to cardiovascular disease</td>
<td>150 (4.8)</td>
<td>150 (4.8)</td>
<td>1.00 (0.87 - 1.13)</td>
<td>0.91</td>
</tr>
<tr>
<td>Mortality: death due to other causes</td>
<td>75 (2.3)</td>
<td>75 (2.3)</td>
<td>1.00 (0.75 - 1.33)</td>
<td>0.94</td>
</tr>
<tr>
<td>Urogenital side effects</td>
<td>89 (2.8)</td>
<td>89 (2.8)</td>
<td>1.00 (0.76 - 1.32)</td>
<td>0.94</td>
</tr>
<tr>
<td>Nonsistent death, death from unknown cause</td>
<td>280 (9.0)</td>
<td>280 (9.0)</td>
<td>1.00 (0.85 - 1.16)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

*For all major outcomes, no patients who underwent randomization with the exception of the events due to death and cardiovascular disease.

**For deaths in patients who underwent randomization without the exception of the events due to death and cardiovascular disease.

***The 95% confidence intervals are calculated based on the log-rank test.

CARES summary

- Among patients with gout and cardiovascular disease, no difference between allopurinol and febuxostat in regards to overall rates of major adverse cardiovascular events.
- Higher all-cause mortality with febuxostat vs. allopurinol.
- Probably due to an imbalance in cardiovascular deaths.
- Major limitations including high drop-out and lost-to-follow up rates.
- Gives pause to using these medicines in patients with significant cardiovascular disease.

Febuxostat: Summary

- More potent than 300 mg/day allopurinol (but many patients can tolerate higher doses of allopurinol).
- As it is not a purine: Appropriate for patients with allopurinol hypersensitivity.
- Can be used safely in patients with mild renal insufficiency (unlike allopurinol).
- Safety signals have emerged particularly in patients with cardiovascular disease – FDA suggests using drug in patients in tolerant or refractory to allopurinol.
Treating severe, refractory tophaceous gout

Lifetime of standard uric acid lowering treatment won’t eliminate these tophi

Uricase

- Enzyme that converts insoluble uric acid to more soluble metabolite allantoin
- Most of animal kingdom (& many mammals) possess uricase, but not humans have lost gene function
- Rasburicase: a drug derived from aspergillus used to treat tumor lysis syndrome in pediatric leukemia
- Rasburicase is extremely immunogenic, which limits its half life and use in chronic diseases

Pegloticase (FDA approval Sept. 2010)

- Mammalian uricase
- Pegylated
  - Increases half life
  - Reduces immunogenicity
- Administered by IV infusion every 2 weeks

Purine Metabolism

Nature Reviews Drug Discovery
Efficacy of Pegloticase
Sundy et al. A&R 2008

- Phase 2 randomized open label dose ranging study 41 patients with serum urate >8
- Intolerance or inadequate response to standard urate lowering therapy (UA>6) for at least 3 months
- Plus one of the following:
  - At least one tophus
  - At least one flare in last 6 months
  - Chronic gouty arthropathy

Visible Results

Pegloticase: Not holy grail

- Infusion reactions (not human)
- Many patients develop antibodies to drug that increases its clearance and diminishes its efficacy
- Anaphylaxis
- 80% patients had gout flares despite prophylaxis
- Contraindicated in G6PD deficient patients
- May exacerbate CHF
### Pegloticase: Summary

- Effective agent for acute lowering and chronic reduction in serum uric acid levels
- Serum uric acid levels are low enough in some patients to promote tophus resorption
- Medication is expensive, immunogenic, and associated with adverse events
- Refer these patients with severe tophaceous gout to rheumatologists!!

### Uric Acid – a perfect “Danger” signal

- Innate immune system recognizes “danger signals” – general molecular structures shared by many different non-human infectious agents
- Recognition of “Danger” is immediate, unlike antigen-specific responses of the adaptive immune system that can take a few weeks to gather momentum (think about timing of vaccines)
- Key participant of innate immunity: The macrophage which can be pre-loaded with an inactive pro-cytokine called Pro-IL-1
- With the right danger signal, an enzyme complex is quickly assembled that can RAPIDLY process Pro-IL-1 into active IL-1β – immediate response to “danger”
- Uric Acid is a perfect danger signal – when cells are infected and die, they release DNA and purines that get metabolized to uric acid
- Uric acid can activate the NLRP3 inflammasome – which processes pro-IL-1 to active IL-1β

### A gout secret formulary managers don’t want you to know about.......

- Plausible targets of inflammatory pathways in gout amenable to biological therapy
- Indeed, biological therapy for acute and chronic gout-related inflammation is available but not FDA approved
- Therapy is highly effective but best reserved for those severe refractory or intolerant patients to conventional therapy

### Gout Therapy: The Future

- Inflammation in gout amenable to biological therapy
- Indeed, biological therapy for acute and chronic gout-related inflammation is available but not FDA approved
- Therapy is highly effective but best reserved for those severe refractory or intolerant patients to conventional therapy

Uric acid can activate inflammasome leading to production and release of IL-1b

Perhaps best evidence yet of anti-IL1 directed therapy for Gout: reduction in future flares

- Secondary analysis of the CANTOS trial
- 10,000+ patients with hx of MI and CRP > 2 mg/dl randomized to several doses of canakinumab (anti-IL1) or placebo
- Reduced risk of composite CV event or death, increased risk of death from infection, no overall difference in mortality

CANTOS: Reduction in gout flares in patients

Not Quite Ready for Prime Time

FDA rejects expanded use of Regeneron drug for gout

Regeneron Pharmaceuticals Inc said U.S. regulators have denied approval for it to expand use of its Ansrol drug to prevent gout flares, asking that the company provide more clinical data. The rejection follows a unanimous vote against the drug's approval in early May by advisors to the U.S. Food and Drug Administration, with panel members expressing concern that the company had only done a 16-week study.
Advances in Therapies for Gout: Summary

• Gout is an ancient disease for whom modern therapy is finally available
  • Should be managed effectively by internists and PCPs who use treat to target approach (not in ACP guidelines)

• New therapies are available
  • Febuxostat (allopurinol refractory, intolerant, or contraindicated)
  • Pegylated uricase: severe tophaceous disease
  • Off-label IL-1 directed therapy

• Rheumatology referral appropriate for difficult to manage cases

The future is bright for those with gout who do not go extinct

Extra Slides

Back to our Challenging Case....

• He has chronic swelling, synovitis, and deformities reminiscent of rheumatoid arthritis
  • Numerous tophi scattered on arms, legs, and ears
  • Serum creatinine is 1.8
  • Uric Acid 10.2
  • Diabetes
Managing the Acute Symptoms

In the acute setting, the best approach to managing this patient’s symptoms would be to start:

A. Indomethacin 75 mg-100mg PO TID
B. Colchicine 0.6 mg PO q2hr until he improves
C. Prednisone 20 mg PO QD
D. Allopurinol 300 mg PO QD

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Managing the Acute Symptoms

A. Indomethacin 75 mg-100mg PO TID
• Can’t use because of renal disease
B. Colchicine 0.6 mg PO q2hr until he improves
• Not standard of care for acute gout
C. Prednisone 20 mg PO QD
• Best choice, but not ideal given diabetes
D. Allopurinol 300 mg PO QD
• Not used to treat acute inflammation

Are there any anti-inflammatory treatments on the horizon for those refractory to or intolerant of standard therapy??

Therapy for Acute Gout: A “Biologic” Future??
Target #2: The Inflammasome

Gout pathogenesis:
• Super saturated serum levels of uric acid lead to crystal formation and deposits in joints
• Crystals are engulfed by macrophages
• Macrophages release inflammatory cytokines
• Recruit more inflammatory cells and perpetuate joint inflammation

How do inert UA crystals lead to inflammation?
How does uric acid lead to inflammation???

- Innate Immune System:
  - Inflammatory cells can innately recognize common microbial features as danger signals
  - Flagella, viral RNA, etc.
  - Leads to rapid inflammation (even septic shock) that acts as "speed bump" until adaptive immune response kicks in
  - Microbial patterns bind to Toll-like receptors and lead to production of pro IL-1

Uric Acid – a perfect “Danger” signal

- Under certain conditions, macrophages are pre-loaded with an inactive pro-cytokine called Pro-IL-1
- With the right danger signal, an enzyme complex is quickly assembled that can RAPIDLY process Pro-IL-1 into active IL-1
- One mechanism by which the innate immune system can slow down pathogens before antigen specific adaptive immunity has chance to catch up
- Uric Acid is a perfect danger signal - when cells are infected and die, they release DNA and purines that get metabolized to uric acid
- Uric acid can activate the NLRP3 inflammasome

Uric acid can activate inflammasome leading to production and release of IL-1b

Dual activation of pattern receptors PLUS a host danger signal (Uric Acid)
Is IL-1 Blockade Effective for Gout?

- IL-1 blockade via:
  - IL-1 Receptor antagonist (Anakinra, commercially available for Rheumatoid Arthritis)
  - Anti-IL-1 antibody (Canakinumab, commercially available to treat certain periodic fevers)
  - IL-1 decoy receptor fusion protein (Rilanocept, commercially available to treat certain periodic fevers)

- Several pilot studies suggest these all work!

- Single dose of Canakinumab superior to triamcinolone injection (has long half life)

Canakinumab (CK) vs. Triamcinolone

- CK administered as one of 5 single doses:
  - Previous gout flare
  - Acute gout flare <5 days
  - Inability to take other acute gout therapy

- Primary endpoint: find dose of CK equivalent to triamcinolone for reduction of pain at 72 hours

- No equivalent dose! All canakinumab doses superior to triamcinolone at 72 hours

Time to First Gout Flare

Secondary endpoints:
- 4 week reduction in gout flares
- Time to 50% reduction in pain
- Reduction in serum inflammatory markers
- Patient and physician global assessments
- Use of other gout therapies

Renal excretion of uric acid

Hyperuricemia
Chronic Gout: Uricosuric agents

• Probenecid: An old friend
  – Uricosuric agent blocks tubular re-absorption of uric acid
  – Useful in patients who under-excrete uric acid (90%)
  – If need be, confirm under-excretion with 24 hr. uric acid <800 mg/24 hrs.
  – Do not use if:
    • Tophi
    • Renal insufficiency
    • Older overproduction syndrome

Lesinurad

• FDA approved 2016 uricosuric for use in combination with xanthine oxidase inhibitor (allopurinol or febuxostat) to lower uric acid
• Useful add-on therapy in treat to target scenario
• Similar contraindications and limitations to probenecid in kidney disease (use with allopurinol is required)