Objectives

- Identify potentially reversible risk factors associated with hyperuricemia
- Develop a safe and effective approach to the treatment of acute gouty arthritis
- Recognize the indications and options for the chronic treatment of symptomatic hyperuricemia
- Identify the importance of treating to target
- Become aware of new and novel treatment options
Who gets gout?

- ~6 million people in the US
- Men, ages 40-50, > than women
- Family connection
- Higher risk:
  - Diabetes
  - High cholesterol
  - High blood pressure
  - Kidney problems

Gout

- Most common cause of inflammatory arthritis in men
- Third National Health and Nutrition Examination Survey (NHANES III):
  - Prevalence: >2% in men >30 and women >50
  - Over 80 years: 9% in men and 6% in women
- Rochester Epidemiologic Project:
  - Incidence of primary gout has doubled over the past 20 years
  - Likely due to dietary and lifestyle trends, and increasing prevalence of obesity and metabolic syndrome
    (Arromdee E et al. J Rheumatol 2002; 29:2403)
Pathogenesis

Stages
1. Prolonged hyperuricemia
2. Formation of MSU crystals
3. Interaction between MSU crystals and the inflammatory system

- Remains uncertain with respect to pace of MSU crystal growth in vivo
  - Based upon in vitro studies, it occurs slowly over months

Hyperuricemia

- Uric acid concentrations are age and gender dependent:
  - Puberty in males
  - Menopause in females
- Males > 7.0 mg/dl; Females > 6.0 mg/dl
- Only 15% of all patients with hyperuricemia develop gout; 30%-50% if their serum uric acid level is > 10 mg/dl
Lifestyle modifications

- Limited efficacy with respect to achieving target
- Weight and alcohol reduction – greatest value
  - Rarely lead to more than 15% reduction in plasma urate
  - Ex: SUA 10.9 – dietary modifications/weight loss – would lead to a reduction of 1.4 = 9.3
  - Obese man who drinks a lot of beer has the potential to reduce plasma urate substantially more than a slim person who drinks alcohol only occasionally

- Small benefit from regular low fat milk and yogurt, soy beans and vegetable proteins, and cherries
- Restricted intake of high purine foods, liver, kidneys, shellfish, yeast extracts, total protein and red meat

**Before requesting substantial lifestyle changes consider low likelihood of benefit & risk that increasing complexity of treatment may reduce compliance with effective drug tx**
Factors

- Hyperlipidemia, HTN, excessive ETOH, obesity and disturbed carbohydrate metabolism with insulin resistance – all common
- Gout and hyperuricemia are associated (independent of traditional CV risk factors) with a higher risk of death from CVD
- Coexistence of impaired renal function or hepatic function and gout has implications to treatment

Stage 1: Hyperuricemia

- Urate solubility is influenced by
  - Temperature
  - pH
  - Sodium concentration
  - Other ions and proteins
- Saturation occurs above 7 mg/dL
- At levels of 8 mg/dL or greater, MSU is more likely to precipitate in tissues.
- Plasma urate level = balance of formation & excretion
- Impaired renal clearance is the predominant factor in >90% of hyperuricemic persons
Stage 2: Gout attack

The Spiral of Gout

Attack Starts

- Proteins lower pH making it possible for more crystals to form
- Proteins ‘call in’ more white blood cells and cause inflammation/pain

Crystals Form

White blood cells attack

Crystals ‘pop’ the cell

Cell releases proteins
Acute Gouty Inflammation: Critical Roles of NALP3 and IL-1beta

NALP3--IL-1beta also central with CPPD crystals, asbestos, and silica and in familial cryopyrinopathy auto-inflammatory syndromes

Diagnosis

- Baseline labs should include:
  - CBC, UA, serum Cr, serum uric acid (SUA).
- Radiography not very useful in initial attacks of acute gouty arthritis. Often helpful in chronic gout.
- Classic radiologic features:
  - tophi, an overhanging edge of cortex and a "punched-out" erosion of bone with sclerotic borders
- Acute crystal-induced arthritis due can present in identical fashion to septic arthritis
- Critical investigation = synovial fluid analysis
Diagnosis

• Synovial fluid can be immediately viewed for evidence of crystals and sent for: cell count, gram stain with cultures and crystals
• In patients with gout, aspiration of fluid from a previously uninvolved joint can demonstrate MSU crystals in 25%
• Plasma urate at time of presentation with acute gout may be misleading.
  o Patients with hyperuricemia – 25% will develop gout. Therefore a raised SUA does not make the diagnosis
  o Approx 40% of persons will have SUA below saturation at the time of flare
  o Mechanism remains unclear
Acute Gout

• Acute Gouty Arthritis
  o Nonsteroidal anti-inflammatory drugs (NSAIDs)
  o Colchicine
  o Corticosteroids (intra-articular or systemic)
  o Analgesics with observation

• With respect to efficacy
  o Rapidity with which tx is started appears more important than which medication is used
  o “Pill-in-the-pocket” strategy should be considered
  o Best choice often is based upon whether or not there are contraindications to NSAID use (renal, cardiac, PUD/UGI bleed)

NSAIDs

• Indomethacin: 50 mg qid x 1d, 50 mg tid x1-2d, 25 mg qid x 1-2d, 25 mg tid x 2-3 d, taper
• Most NSAIDs effective: use maximum dose as soon as the attack occurs
• Contraindications: bronchospasm, PUD, CRI, hepatic insufficiency, severe CHF, warfarin therapy
• Use with caution: mild renal insufficiency, h/o PUD, IBD, unstable CAD or HTN
Colchicine

• Acute regimen:
  o Most effective within 24 hr of an attack
  o Colchicine 1.2 mg followed by 0.6 mg in 1 hour
  o Incidence of N/V/D less with the low-dose regimen vs old high-dose regimen
• Mild to moderate (Clcr 30-50 mL/min) renal impairment, dose adjustment not required
• Severe impairment, while the dose does not need to be adjusted for the treatment of gout flares, a treatment course should NOT be repeated more than once every two weeks
• For patients undergoing dialysis, the total recommended dose for the treatment of gout flares should be reduced to a single dose of 0.6 mg (one tablet)

Corticosteroids

• Intra-articular
  o It is reasonable to administer intra-articular steroids immediately following joint aspiration when gout appears likely
  o Send synovial fluid for analysis
• Prednisone can be provided as oral 20-40 mg daily in divided doses reducing to zero in 10-14 days
Stage 3: Between attacks

- The time between gout attacks
  - Aka as "intercritical gout."
- Even when patients aren't experiencing painful flares, they still have gout
- MSU crystals are still present in the joints for as long as the target SUA (<6) has not been reached
- Joint damage may still continue even between gout flares

Stage 4: Chronic gout

- Final phase
  - Aka as "chronic tophaceous gout"
  - The most disabling phase of the disease.
- Over time, the period between gout attacks may disappear, leaving behind constant joint inflammation, joint deformity, and deposits of crystallized uric acid (tophi).
- Tophi can cause chronic and persistent pain, joint destruction, damage surrounding tissues, and may also lead to deformities.
- And you can still have painful gout attacks even during this uncomfortable period!
Prophylaxis

- NSAIDs, colchicine, low dose steroids
- Aim is to prevent attacks, to prevent joint/bone damage and to prevent other sequelae of tophi
- Fewer flares, faster reduction in tophi and depletion of MSU crystals
- Goal – SUA < 6; lower target may be necessary

Colchicine

- Used to prevent recurrent attacks of gout or when starting ULT (24% risk of precipitating an acute gouty attack)
- Dosage:
  - Normal renal and hepatic function: 0.6 mg po bid
  - Elderly or CrCl 30-50: 0.6 mg po qd or qod
  - CrCl < 30: avoid acute or prophylactic therapy
  - Avoid in hemodialysis and in severe hepatic dysfunction

Terkeltaub RA. Semin Arthritis Rheum 2009;38:411
Prophylactic colchicine dosing guidelines for CKD

Conservative recommendations, with maximal attention to safety (not yet evidence-based):

- Colchicine 0.6 mg po bid with CrCl > 60
- Colchicine 0.6 mg po daily with CrCl 40-59
- Colchicine 0.6 mg q 2 days with CrCl 30-39 (M/W/F)
- Colchicine 0.6 mg q 3 days with CrCl 11-29 or 0.3 mg q 2 days (M/W/F)
- Avoid colchicine therapy with CrCl ≤10 or dialysis

Drug intervention

- Who should be treated?
- When to start Urate Lowering Therapy (aka ULT)?
  - At least 2 flares/year
  - Presence of tophi
  - Radiographic changes of gouty arthropathy
  - Nephrolithiasis
  - Co-morbid conditions which may complicate treatment of gout (CVD, CKD)
- What is our GOAL?
  - SUA < 6 (without tophi)
  - SUA < 5 (with tophi)
# Choosing Among ULTs

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**Uricosurics**

- Inhibits reabsorption of uric acid in the proximal tubules of the kidney
- Indications: underexcretors with adequate renal function not on > 81 mg/day of ASA

**Probenecid**

- Starting dose - 250 mg BID to 1000 mg daily & titrated to max 2000 mg
- Given inappropriately will cause renal stones and urate nephropathy
- Good oral hydration is a MUST

**Contraindications:**
- Can only be used if CrCl > 40 cc/min as below this drug is ineffective
- Age > 65: diminished CrCl
- Uric acid nephrolithiasis or overproducers of uric acid
  - Must have 24 hour urine for uric acid < 800 mg/dl
- ASA usage > 81 mg/day: negates the drug’s uricosuric actions

**Fenofibrate & Losartan** have weak uricosuric effects and may be of some benefit if there is an indication for one of these
Allopurinol

- Non-selective purine
- Inhibits xanthine oxidase, the enzyme converts hypoxanthine to xanthine to uric acid
- Introduction of ULT is associated with a temporary increased risk of flare
  - Administer ONLY with prophylaxis
  - ONLY after acute flare has resolved
  - Start at low dose, titrate slowly
  - Risk of flare reduced by gradual fall in SUA
  - Do not stop during flare
- Vast majority of RX are for doses of 300 mg/day or less and yet only 24% of patients who received allopurinol 300 mg daily reached SUA <6

Hypersensitivity Syndrome

- Severe; mortality rate 18%
- Rare 1 in 56,000
- 95% of cases occur within 6 weeks of initiation
- All age groups
- Association with renal impairment and inc age
- Development of rash or fever during first 3 months of should prompt urgent ER evaluation
- Despite assoc with renal impairment, no increase in the prevalence of adverse reactions seen in pts with higher maintenance doses

Allopurinol

- Check that the patient is not using azathioprine or 6-mercaptopurine (the use of allopurinol or febuxostat with either is potentially dangerous)
- Start Allopurinol 100 mg daily
- Labs every 4 weeks: CBC, Cr, LFTs, SUA
- Titrate allopurinol every 4 weeks in 100 mg increments until SUA <6 or lower
- Doses of 600mg/day not uncommonly required and up to 900 mg/day is occasionally utilized

Allopurinol

- Treatment of gout patients with impairment of renal function: a systematic literature review.
- van Echteld IA, van Durme C, Felton L, Landewé RB, van der Heijde DM, Aletaha D.

RESULTS:
- Eight trials met inclusion criteria. Trials covered treatment with allopurinol, benzbromarone, rasburicase, or febuxostat in a gout population with mild or moderate renal insufficiency. High risk of bias (5/8 trials) and heterogeneously allocated format metaanalysis. The trials showed the following hierarchy in efficacy lowering the SUA below 6.0 mg/dl: febuxostat 80 mg (44%-71%) > febuxostat 40 mg (43%-52%) > allopurinol 100 mg or 200 mg (0-44%) after 6 months of therapy; rasburicase (46%) > allopurinol 300 mg (16%) after 7 days of therapy; benzbromarone 100-200 mg (93%) > allopurinol 100-200 mg (63%) after 9-24 month of therapy. The combination of allopurinol and benzbromarone seemed to be effective, with a significant reduction in the SUA from 7.8 to 5.7 mg/dl (p < 0.05) after 1 month. One study showed that 89% achieved the target SUA using higher doses of allopurinol than usually recommended for patients with renal impairment without an apparent increase in adverse events. In addition, allopurinol and benzbromarone significantly improved renal function.

CONCLUSION:
- In gout patients with renal insufficiency febuxostat and allopurinol seemed to be effective and safe; allopurinol may be cautiously titrated until the target uric acid level has been reached, and may improve renal function.
Novel non-purine xanthine oxidase inhibitor:
Febuxostat

- Non-purine backbone, selective inhibitor of xanthine oxidase

\[
\begin{align*}
\text{Allopurinol} & \\
\text{Febuxostat}
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- Pertinent Pharmacology
  - Primarily metabolized by oxidation and glucuronidation in the liver
  - Unlike allopurinol has no effect on pyrimidine metabolism and is not reincorporated into nucleotides

Febuxostat

- FACT (2005)
- APEX (2008)
- FOCUS (2009)
- EXCEL (2009)
- CONFIRMS (2010)

Febuxostat FACT Trial
Magnitude of Urate Reduction

Percent of Subjects

FBX 80  FBX 120  ALLO 300

<6 mg/dl  <5 mg/dl  <4 mg/dl


Febuxostat

• Non-purine analogue. Xanthine oxidase inhibitor
• Dosing: 40 mg/d with ↑ to 80 mg if needed for goal SUA
• Metabolized mainly in the liver; allopurinol metabolites are renally excreted
• Can be used in mild CKD 2 to moderate CKD 3 (CrCl 30-59 ml/min); data in CKD 4 not yet published
• Very effective
  o 93% of patients who tolerated and continued for 5 years achieved target
  o In a 28 day study, those who reached target
      • Placebo 0%
      • 40 mg/day 56%
      • 80 mg/day 76%
      • 120 mg/day 94%
  Flares more common in 80mg/day (43%) and 120mg/day (55%) without prophylaxis
  Only 8%-13% with colchicine prophylaxis (0.6 twice daily)

• Safety
Chronic Tophaceous Gout
Tophi

Monosodium Urate Crystal

Uricase enzymes

- Uricase (uric acid oxidase) catalyzes the conversion of uric acid to allantoin
  - A more soluble and readily excretable form

\[
\text{Uricase} \quad \text{Uric acid} \quad \text{H}_2\text{O} + \text{O}_2 \quad \text{Allantoin} \quad \text{H}_2\text{O}_2 \quad \text{CO}_2
\]
Pegloticase

- Pegylated, recombinant uricase
- Before starting, screen for G6PD deficiency
- G6PD deficiency is an exclusion criterion for treatment due to the risk of hemolysis and methemoglobinemia.
- Discontinue oral urate-lowering agents before starting
- Monitor SUA before each infusion
  - Loss of urate lowering response indicates development of anti-pegloticase abs and requires cessation of therapy; ↑ risk infusion reactions
- Patients should be pre-medicated with antihistamines and corticosteroids
- Administer in a healthcare setting by healthcare providers prepared to manage anaphylaxis
- Dose: 8 mg IV infusion every two weeks

- First few months: 80% acute gout flares that taper off

Pegloticase (Krystexxa™) Phase 2 Data
Pegloticase Phase 2 Data


Pegloticase q 2 weeks 45% pts with resolution of target tophus at week 25

Figure from Sherman M, et al, Adv Drug Deliv Res, 2008
Comparison of Tophus De-bulking Effects Pegloticase and Allopurinol

Pegloticase Phase 3 Trials: ~70% with tophi
• 20% resolved at 13 weeks
• 40% resolved at 25 weeks

Febuxostat/Allopurinol Trials: ~30% with tophi
• 50-80% reduction of tophus size by 1 yr
• ~50% resolved by 2 years with febuxostat


Acute Gouty Inflammation:
Critical Roles of NALP3 and IL-1beta

NALP3→ IL-1beta also central with CPPD crystals, asbestos, and silica and in familial cryopyrinopathy auto-inflammatory syndromes
Free MSU crystals ↓
C5b-9, Synoviocyte, mast cell, endothelial activation
**IL-1β, TNFα, IL-6, histamine**
**IL-8 & GRO chemokines, CXCL16**
↓
Local and systemic inflammation
Monocyte and neutrophil influx
Amplification of synovitis by neutrophils
(S100A8/9, **IL-1β**, chemokines)

Anakinra

- **IL-1 receptor antagonist**

- **Dosing:**
  - 100 mg subcu daily x3
  - Resolution of acute gout in 9/10 patients
Efficacy of anakinra in gouty arthritis: a retrospective study of 40 cases


Abstract

Introduction: Gout is a common arthritis that occurs particularly in patients who frequently have associated conditions that limit the use of conventional therapies. The main mechanism of crystal-induced inflammation is interleukin-1 production by activation of the inflammasome. We aimed to evaluate the efficacy and tolerance of anakinra in gouty patients.

Methods: We conducted a multicenter retrospective review of patients receiving anakinra for gouty arthritis. We reviewed the response to treatment, adverse events and relapses.

Results: We examined data for 40 gouty patients (37 men, mean age 66.0 ± 13.3 years) receiving anakinra. Mean follow-up duration was 6.9 ± 6.7 years. All patients treated concomitantly with or without 3 or more conventional therapies. Mean blood levels (0.15 ~ 1.67 μg/L) were found to be effective (≤1.3 mg/L) in patients only in the median delay of 1.1 mg/L to 1.3 mg/L. Relative effects occurred in 13 patients after a median delay of 1.0 mg/L to 1.2 mg/L days. Seven infectious events, mainly with long-term use of anakinra, were noted.

Conclusions: Anakinra may be efficient in gouty arthritis, is relatively well tolerated with short-term use, and could be a relevant option in managing gouty patients when conventional therapies are ineffective or contraindicated. Its long-term use could be limited by infectious complications.

Keywords: gout, IL-1, anakinra, arthritis

Introduction

Gout is a common arthritis caused by deposition of monosodium urate (MSU) crystals within and around joints secondary to chronic hyperuricemia. It affects 1% to 2% of adults in developed countries and may be increasing in prevalence [1]. Acute gouty arthritis may be associated with high inflammatory clinical and histological symptoms. Thus, one of the goals of management is achieving remission and preventing future acute attacks. Concomitant use of urate-lowering therapies, including uricosuric agents, is recommended along with non-steroidal anti-inflammatory drugs (NSAIDs), colchicine and allopurinol [2]. Gouty patients often have concomitant renal, cardiovascular and gastrointestinal diseases as well as diabetes mellitus [3]. These comorbidities and associated treatments can lead to increased frequency of side effects or contraindications to conventional therapies for gouty arthritis [4]. We have abundant evidence of side effects from the use of colchicine (for example, diarrhea) [5] and NSAIDs (for example, gastrointestinal bleeding, cardiovascular events including myocardial infarction, peptic ulcer disease, and acute renal failure) [6]. Therefore, alternative therapies should be taken when prescribing such drugs. Thus alternative therapies are needed for these arthritis patients.

Treatment of Acute Gouty Arthritis in Complex Hospitalized Patients with Anakinra

Pradip Patel, Michael Chiu, Gurpreet Kaurat, Peter A. Simkin, and Gregory C. Aarons

Objective: To report our experience with the efficacy and safety of anakinra for acute gouty arthritis in medically complex hospitalized patients.

Methods: We reviewed the hospital charts of 20 patients treated with anakinra for crystal-induced arthritis since 2007. Demographics, comorbid conditions, reason for anakinra use, response to treatment, and any adverse outcomes were assessed.

Results: Twenty-six patients received 48 courses of anakinra therapy. In 67% of patients, pain improved significantly within 24 hours of treatment, and complete resolution of signs and symptoms of gout occurred by day 3. In 32% of patients, severe patients received multiple courses with no decrement in response with repeated treatments. Anakinra was well tolerated and no adverse events were attributed to the medication. Only 1 patient appeared to be refractory to this form of interleukin-1 inhibition.

Conclusions: Anakinra is an effective and safe alternative treatment for acute gouty arthritis in medically complex hospitalized patients who fail or cannot undergo more conventional therapy.

Introduction

Gout is a chronic inflammatory disease mediated by monosodium urate crystals and characterized by recurrent attacks of monosodium urate or poikilothermia. Gouty inflammation commonly occurs during the first 24 hours following hospitalization, and can also be precipitated by arthrosis or medications such as diuretics. The hallmark of gouty arthritis is the arthritic inflex of monosodium crystals on the joint. Gouty arthritis is a common disease and can lead to disability. The treatment for acute gouty arthritis has not changed in many years. Standard therapy includes non-steroidal anti-inflammatory drugs (NSAIDs), and in some cases, colchicine. Some patients respond poorly to these therapies, and they may be safely utilized due to potential medical conditions. Given the pathophysiologic mechanisms for IL-1 inhibition by monosodium urate crystals, IL-1 inhibition can be an appealing therapy for gouty arthritis. In a study of 10 patients with gout who had failed standard gout medications, treatment with 180 mg daily for 3 days with the IL-1 receptor antagonist anakinra was associated with rapid and marked improvement in signs and symptoms of inflammation [4]. In addition,
**Key points**

- **Lifestyle modifications are recommended.**
- **Assess the patient’s comorbid medical conditions including renal and hepatic function to guide the safest treatment options for acute gout and symptomatic hyperuricemia with goal SUA < 6.0 mg/dl.**
- **Acute gout (pill-in-the-pocket):** NSAIDs, colchicine, corticosteroids
- **Indications for lifelong ULT:**
  - 2 or more gout attacks/year
  - Tophaceous gout
  - Uric acid renal stones
- **Never start, stop, or adjust ULT during an acute flare.**
Key points

- Urate lowering therapy:
  - Start low and gradually titrate to goal sUA
  - Prophylaxis for at least 6-12 months during titration
- Treat to target SUA <6; lower if tophi or unable to discontinue prophylactic agent without flare
- Febuxostat:
  - Intolerant to allopurinol or difficult to achieve target
  - CKD with CrCl > 30 ml/min; no dose adjustment needed
- Pegloticase: refractory to conventional ULT or need for debulking the urate load
- Anakinra

Basic recommendations

- Colchicine 0.6 mg PO daily/BID for prophylaxis
- Continue Colchicine 0.6 PO daily/BID solo for two weeks
- Add Allopurinol to Colchicine regimen - begin Allopurinol 100 mg PO daily
- Labs should be obtained every 4 weeks to include CBC, Cr, LFTs and uric acid.
- Titrate Allopurinol in 100mg increments every 4 weeks to a maximum dose of 300-450 mg PO BID until goal serum uric acid <6 is reached.
- DO NOT DISCONTINUE ALLOPURINOL DURING FLARE. Simply treat with PO steroids through the flare.
- An example of a steroid regimen would include 40 mgx3d, 30mg x3d, 20mgx3d, 15mgx3d, 10mgx3d, 5mgx3d then stop.
- Goal is to achieve serum uric acid (SUA) <6. Some patients require a target SUA <5 to prevent recurrent flares. The patient will likely continue to flare until this goal is achieved. He/she should be warned that he/she still could flare if he ingests purine rich foods or alcohol; or if he becomes dehydrated.
- When treatment goal (SUA <6) is achieved for 3 consecutive months the Colchicine may be discontinued.
- If you find that the patient does not reach treatment goal with further titration of Allopurinol, please submit a NEW Rheumatology consult at which time we will consider the patient for alternative treatment options.