Gout: Beyond the Basics

JENNIFER A. BRACKNEY, DO, FACOI, FACR
RHEUMATOLOGY
VA PITTSBURGH HEALTHCARE SYSTEM

LECOM Primary Care Conference
August 16, 2015

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
    (Kramer HM et al. Am J Kidney Dis 2002;40:37)
- 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

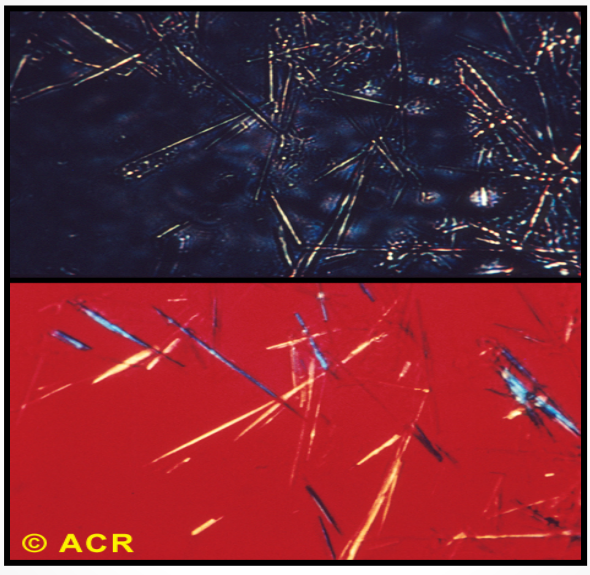
Hyperuricemia

- 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
- *Asymptomatic hyperuricemia* does not require treatment (Mikuls TR et al. Arthritis Rheum 2004;50:937)

Lifestyle modifications

- Limited efficacy with respect to achieving target
- Weight and alcohol reduction – greatest value
  - Rarely lead to more than 15% reduction is plasma urate
  - Ex: SUA 10.9 – dietary modifications/weight loss – would lead to a reduction of 1.6 = 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 occ
- 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



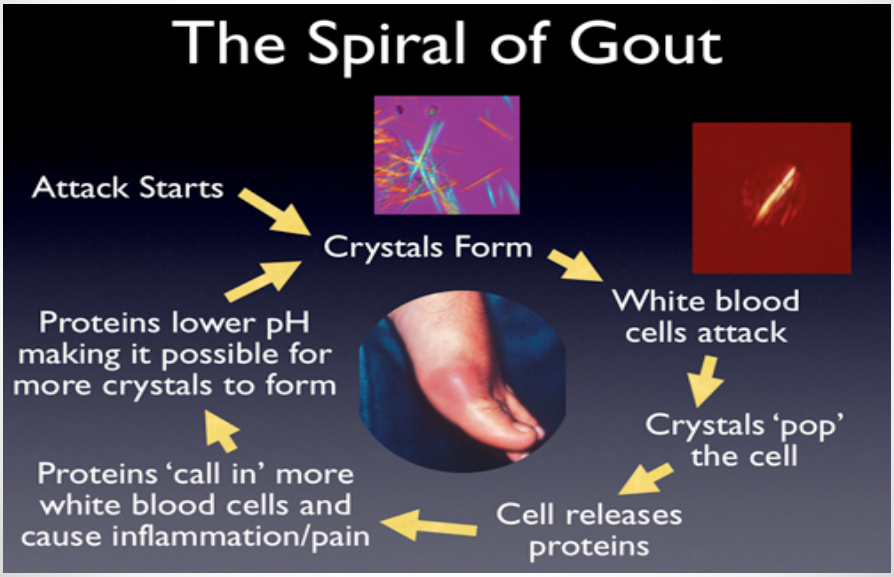
Factors

- 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

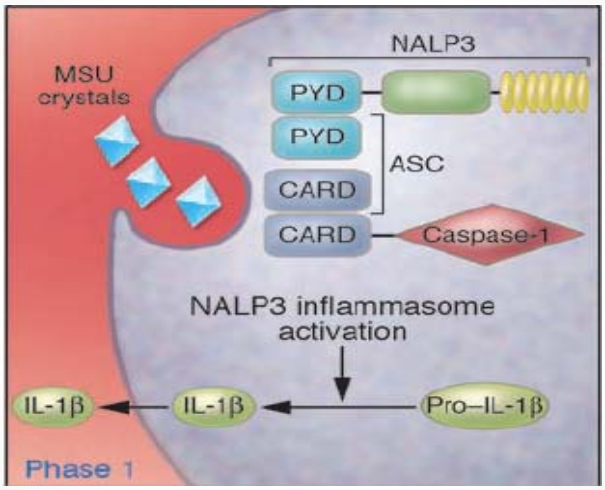
Stage 1: Hyperuricemia

- 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



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



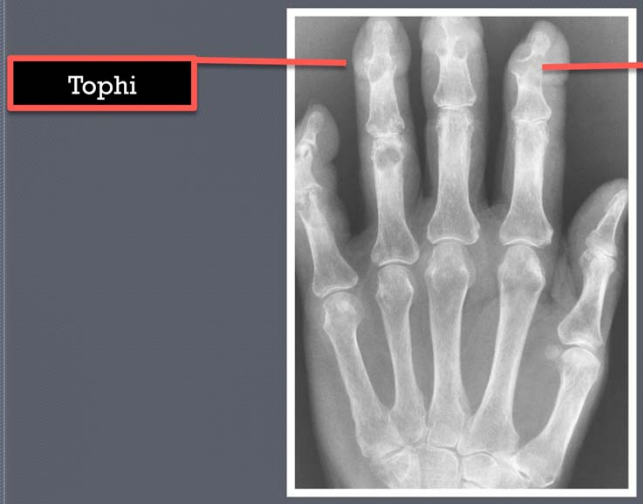
Martinon et al JCI, 2006

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

Gout
X Ray Findings



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.
  - Patients with hyperuricemia – 25% will develop gout. Therefore a raised SUA does not make the diagnosis
  - Approx 40% of persons will have SUA below saturation at the time of flare
  - Mechanism remains unclear

Acute Gout

- Acute Gouty Arthritis
  - Nonsteroidal anti-inflammatory drugs (NSAIDs)
  - Colchicine
  - Corticosteroids (intra-articular or systemic)
  - Analgesics with observation
- With respect to efficacy
  - Rapidity with which tx is started appears more important than which medication is used
  - **"Pill-in-the-pocket" strategy should be considered**
  - 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:
  - **Most effective within 24 hr of an attack**
  - **Colchicine 1.2 mg followed by 0.6 mg in 1 hour**
  - **Incidence of N/V/D less with the low-dose regimen vs old high-dose regimen**

    Terkeltaub RA et al. Arthritis Rheum 2010;62:1060
- 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
  - It is reasonable to administer intra-articular steroids immediately following joint aspiration when gout appears likely
  - 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

URICOSURICS	XANTHINE OXIDASE INHIBITORS	URICASE
Probenecid	Allopurinol Febuxostat	Pegloticase
Losartan Fenofibrates		

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 to1000 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

Vazquez J, et al. Ann Rheum Dis 2001; 60: 981-3

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
- Reports of no association between dose and risk of hypersensitivity syndrome/toxicity (Dalbeth N et al. J Rheumatol 2006;33:1646 / Stamp LK et al. Arthritis Rheum 2011;63:412)

Allopurinol

- J Rheumatol Suppl. 2014 Sep;92:48-54. doi: 10.3899/jrheum.140462.
- **Treatment of gout patients with impairment of renal function: a systematic literature review.**
- van Echteld IA[1], van Durme C[2], Falzon L[2], Landewé RB[2], van der Heijde DM[2], Aletaha D[2].

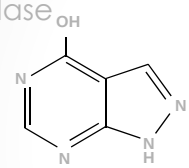
- **RESULTS:**
- Eight trials met inclusion criteria. Trials covered treatment with allopurinol, benzbromarone, rasburicase, or febuxostat in a gout population with mild or moderate renal insufficiency. High risk of bias (5/8 trials) and heterogeneity precluded formal metaanalysis. The trials showed 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 (0-46%) 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 months 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.**

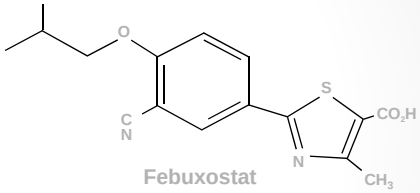
Novel non-purine xanthine oxidase inhibitor:

Febuxostat

- Non-purine backbone, selective inhibitor of xanthine oxidase



Allopurinol



Febuxostat

- 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

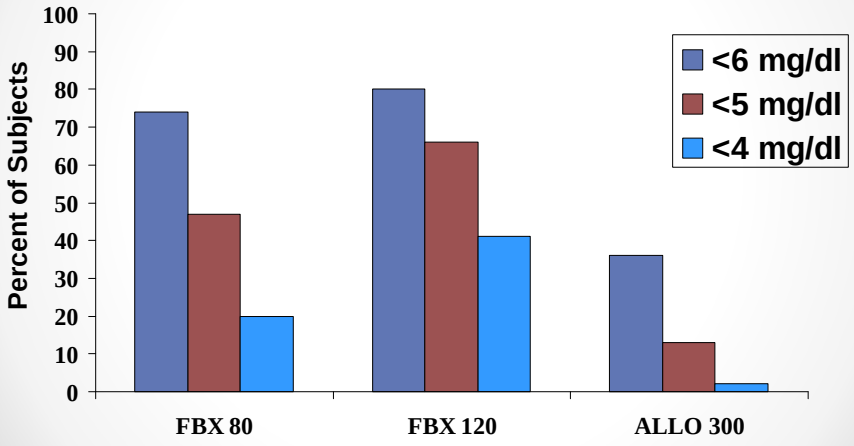
Febuxostat

- FACT (2005)
  - Becker MA, Schumacher HR, et al. NEJM 2005; 353 (23): 2450-61
- APEX (2008)
  - Schumacher HR, Becker MA, et al. Arth Rheum 2008; 59 (11); 1540-8
- FOCUS (2009)
  - Schumacher HR, Becker MA, et al. Rheum 2009; 48: 188-94
- EXCEL (2009)
  - Becker MA, Schumacher HR, et al. J Rheum 2009; 36 (6): 1273-82
- CONFIRMS (2010)
  - Becker MA, Schumacher HR, et al. Arth Res Ther 2010; 12 (2): R63

Tayar JH et al. Febuxostat for treating chronic gout. Cochrane Database of Sys Rev 2012; 11: Art No CD008653

Febuxostat FACT Trial

Magnitude of Urate Reduction

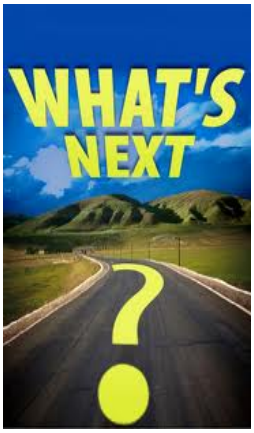


Becker, M. A. et al. N Engl J Med 2005;353:2450-2461

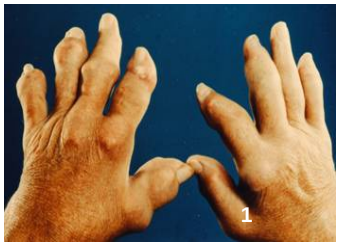
Febuxostat

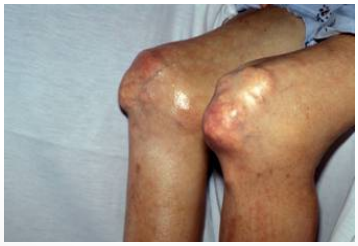
- Non-purine analogue. Xanthine oxidase inhibitor
- Dosing: 40 mg/d with ↑ to 80 mg if needed for goal SUA
- **Metabolized mainly in the liver; allopurinol metabolites are renally excreted**
- Can be used in mild CKD 2 to moderate CKD 3 (CrCl 30-59 ml/min); data in CKD 4 not yet published
- Very effective
  - 93% of patients who tolerated and continued for 5 years achieved target
    - Schumacher HR, Becker MA, et al. Febuxostat in the treatment of gout: 5-yr findings of the FOCUS efficacy and safety study. Rheum 2009; 48: 188-94
  - In a 28 day study, those who reached target
    - Becker MA, et al. Arth Rheum 2005; 52: 916-23
      - 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 colchichine prophylaxis (0.6 twice daily)
- Safety

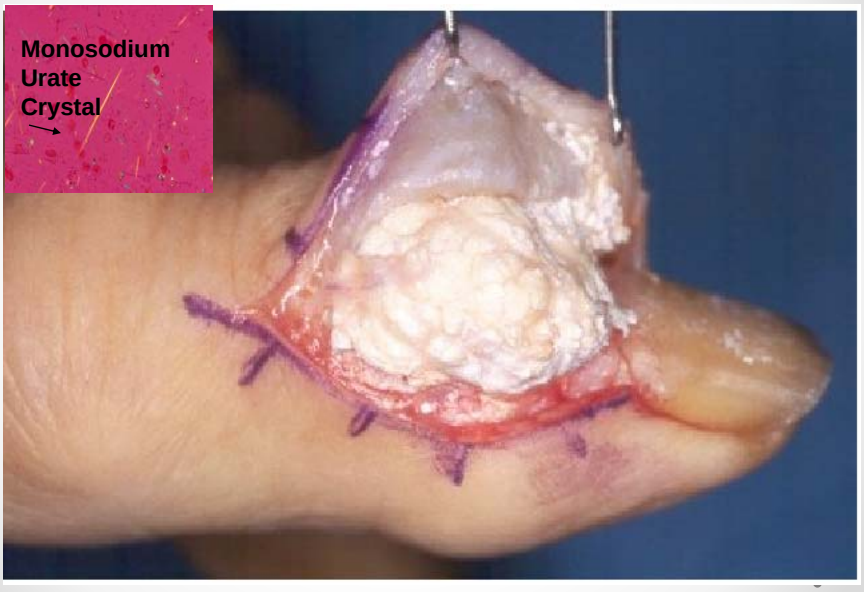


Chronic Tophaceous Gout

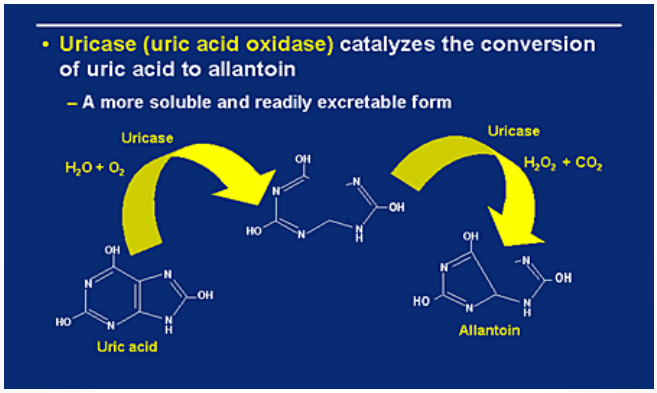




Tophi



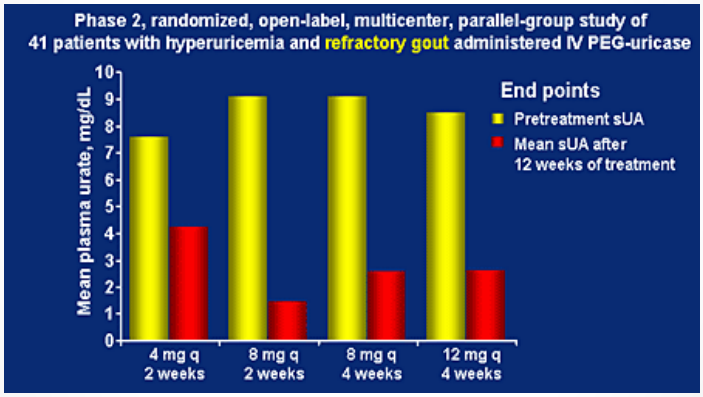
Uricase enzymes



Pegloticase

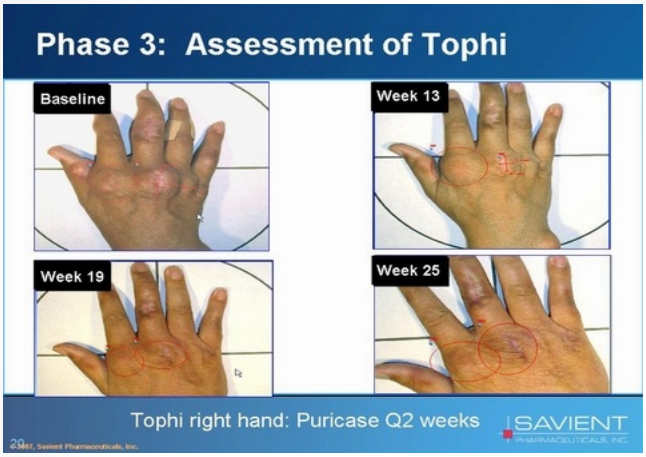
- Pegylated, recombinant uricase
- Before starting, screen for G6PD deficiency
- G6PD deficiency is an exclusion criterion for treatment due to the risk of hemolysis and methemoglobinemia.
- Discontinue oral urate-lowering agents before starting
- Monitor SUA before each infusion
  - Loss of urate lowering response indicates development of antipegloticase 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

Baraf H et al. Arthritis Rheum 2008;58:3632



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

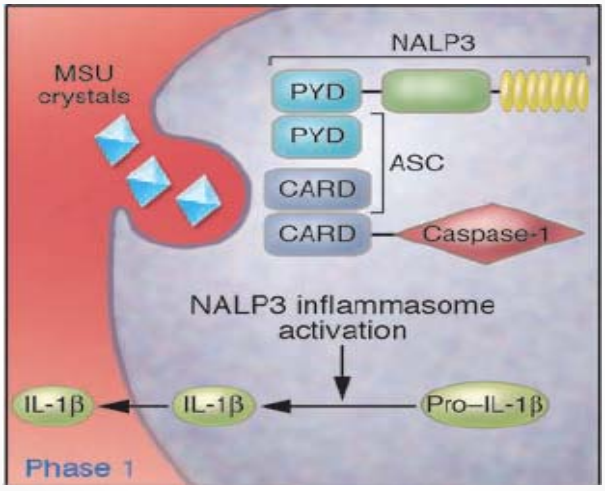
Comparison of Tophus De-bulking Effects Pegloticase and Allopurinol

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

Sundy S et al. Arthritis Rheum 2005;52:S679

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



Martinon et al JCI, 2006

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**

Ottaviani *et al. Arthritis Research & Therapy* 2013, **15**:R123
http://arthritis-research.com/content/15/5/R123

arthritis research&therapy

RESEARCH ARTICLE Open Access

Efficacy of anakinra in gouty arthritis: a retrospective study of 40 cases

Sébastien Ottaviani[1], Anna Moltó[2], Hang-Korng Ea[2], Séverine Neveu[3], Ghislaine Gill[1], Lauren Brunier[1], Elisabeth Palazzo[1], Olivier Meyer[1], Pascal Richette[2], Thomas Bardin[2], Yannick Allanore[4], Frédéric Lioté[2], Maxime Dougados[3] and Philippe Dieudé[1*]

Abstract

Introduction: Gout is a common arthritis that occurs particularly in patients who frequently have associated comorbidities 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 (32 men; mean age 60.0 ± 13.9 years) receiving anakinra. Mean disease duration was 8.7 ± 8.7 years. All patients showed contraindications to and/or failure of at least two conventional therapies. Most (36; 90%) demonstrated good response to anakinra. Median pain on a 100-mm visual analog scale was rapidly decreased (73.5 (70.0 to 80.0) to 25.0 (20.0 to 32.5) mm, P <0.0001), as was median C-reactive protein (CRP) level (130.5 (55.8 to 238.8) to 16.0 (5.0 to 29.5) mg/l, P <0.0001). After a median follow-up of 7.0 (2.0 to 13.0) months, relapse occurred in 13 patients after a median delay of 15.0 (10.0 to 70.0) 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 arthritis 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 biological symptoms. Thus, one of the goals of management is rapid relief of inflammation [2,3].

Acute gouty attacks are usually treated with nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine and corticosteroids [3]. Gouty patients often have concomitant renal, cardiovascular and gastrointestinal diseases as well as diabetes mellitus [4]. 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, for diarrhea) [5] and NSAIDs (for example, for gastrointestinal bleeding, cardiovascular events including myocardial infarction, renal impairment) [6,7], so care must be taken when prescribing such drugs. Thus, alternative therapies are needed for these 'difficult-to-treat' cases.

Arthritis Care & Research
Vol. 65, No. 8, August 2013, pp 1381–1384
DOI 10.1002/acr.21989

BRIEF REPORT

Treatment of Acute Gouty Arthritis in Complex Hospitalized Patients With Anakinra

PRADIPTA GHOSH,[1] MICHAEL CHO,[2] GURPREET RAWAT,[2] PETER A. SIMKIN,[2] AND GREGORY C. GARDNER[2]

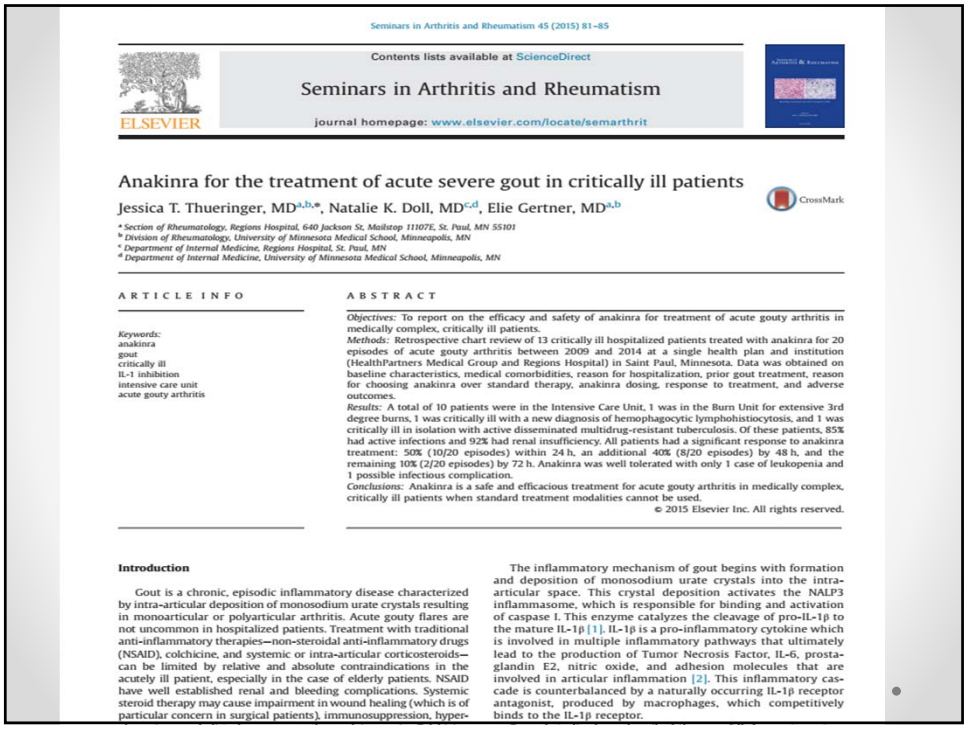
Objective. **To report our experience with the efficacy and safety of anakinra for acute gouty arthritis in medically complex hospitalized patients.**
Methods. **We reviewed the hospital charts of 26 patients treated with anakinra for crystal-induced arthritis since 2007. Demographics, comorbid conditions, reason for anakinra use, response to treatment, and any adverse outcomes were recorded.**
Results. **Twenty-six patients received 40 courses of anakinra therapy. In 67% of patients, pain improved significantly within 24 hours, and complete resolution of signs and symptoms of gout occurred by day 5 in 72.5% of patients. Seven patients received multiple courses with no decrement in response with repeated treatments. Anakinra was well tolerated and no adverse outcomes were attributed to the medication. Only 1 patient appeared to be refractory to this form of interleukin-1 inhibition.**
Conclusion. **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 monarthritis or polyarthritis. Gouty inflammation commonly flares during the bed rest required by hospitalized patients, and also can be precipitated by acidosis or medications such as diuretics. The hallmark of gouty arthritis is the articular influx of neutrophils mediated by cytokines such as interleukin-1β (IL-1β), tumor necrosis factor α, and IL-6 (1,2). Martinon et al showed that monosodium urate crystals as well as calcium pyrophosphate dihydrate crystals can mediate the production of IL-1β via activation of the NALP3 inflammasome (3). The inflammasome is a component of the innate immune system and when activated, binds and activates caspase 1, which in turn cleaves pro–IL-1β into the active cytokine, IL-1β (1). Mice deficient in various components of the inflammasome are unable to mount an inflammatory response to either of these crystals.

Available treatments for acute gouty arthritis have not changed in many years. Standard therapies include nonsteroidal antiinflammatory drugs (NSAIDs), oral or injectable steroids, and oral colchicine. Some patients respond poorly to these therapies and/or they cannot be safely utilized due to comorbid medical conditions. Given the pathophysiologic mechanism for IL-1β activation by monosodium urate crystals, IL-1β inhibition comprises an appealing therapy for gouty arthritis. In a study of 10 patients with gout who had failed standard gout medications, treatment with 100 mg daily for 3 days with the IL-1 receptor antagonist, anakinra, resulted in impressive improvement in signs and symptoms of inflammation (4). In addition,

Supported by an NIH T-32 Training Grant, an American College of Rheumatology Fellowship Training Award, and an Arthritis Foundation Training Grant.
[1]Pradipta Ghosh, MD: Kaiser Santa Clara Homestead Campus, Santa Clara, California; [2]Michael Cho, MD, Gurpreet Rawat, MD, Peter A. Simkin, MD, Gregory C. Gardner, MD:



Seminars in Arthritis and Rheumatism 45 (2015) 81–85

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Anakinra for the treatment of acute severe gout in critically ill patients

Jessica T. Thueringer, MD[a,b,*], Natalie K. Doll, MD[c,d], Elie Gertner, MD[a,b]

[a] Section of Rheumatology, Regions Hospital, 640 Jackson St, Mailstop 11107E, St. Paul, MN 55101
[b] Division of Rheumatology, University of Minnesota Medical School, Minneapolis, MN
[c] Department of Internal Medicine, Regions Hospital, St. Paul, MN
[d] Department of Internal Medicine, University of Minnesota Medical School, Minneapolis, MN

ARTICLE INFO

Keywords:
anakinra
gout
critically ill
IL-1 inhibition
intensive care unit
acute gouty arthritis

ABSTRACT

Objectives: To report on the efficacy and safety of anakinra for treatment of acute gouty arthritis in medically complex, critically ill patients.

Methods: Retrospective chart review of 13 critically ill hospitalized patients treated with anakinra for 20 episodes of acute gouty arthritis between 2009 and 2014 at a single health plan and institution (HealthPartners Medical Group and Regions Hospital) in Saint Paul, Minnesota. Data was obtained on baseline characteristics, medical comorbidities, reason for hospitalization, prior gout treatment, reason for choosing anakinra over standard therapy, anakinra dosing, response to treatment, and adverse outcomes.

Results: A total of 10 patients were in the Intensive Care Unit, 1 was in the Burn Unit for extensive 3rd degree burns, 1 was critically ill with a new diagnosis of hemophagocytic lymphohistiocytosis, and 1 was critically ill in isolation with active disseminated multidrug-resistant tuberculosis. Of these patients, 85% had active infections and 92% had renal insufficiency. All patients had a significant response to anakinra treatment: 50% (10/20 episodes) within 24 h, an additional 40% (8/20 episodes) by 48 h, and the remaining 10% (2/20 episodes) by 72 h. Anakinra was well tolerated with only 1 case of leukopenia and 1 possible infectious complication.

Conclusions: Anakinra is a safe and efficacious treatment for acute gouty arthritis in medically complex, critically ill patients when standard treatment modalities cannot be used.

Introduction

Gout is a chronic, episodic inflammatory disease characterized by intra-articular deposition of monosodium urate crystals resulting in monoarticular or polyarticular arthritis. Acute gouty flares are not uncommon in hospitalized patients. Treatment with traditional anti-inflammatory therapies—non-steroidal anti-inflammatory drugs (NSAID), colchicine, and systemic or intra-articular corticosteroids—can be limited by relative and absolute contraindications in the acutely ill patient, especially in the case of elderly patients. NSAID have well established renal and bleeding complications. Systemic steroid therapy may cause impairment in wound healing (which is of particular concern in surgical patients), immunosuppression, hyper-

The inflammatory mechanism of gout begins with formation and deposition of monosodium urate crystals into the intra-articular space. This crystal deposition activates the NALP3 inflammasome, which is responsible for binding and activation of caspase 1. This enzyme catalyzes the cleavage of pro-IL-1β to the mature IL-1β [1]. IL-1β is a pro-inflammatory cytokine which is involved in multiple inflammatory pathways that ultimately lead to the production of Tumor Necrosis Factor, IL-6, prostaglandin E2, nitric oxide, and adhesion molecules that are involved in articular inflammation [2]. This inflammatory cascade is counterbalanced by a naturally occurring IL-1β receptor antagonist, produced by macrophages, which competitively binds to the IL-1β receptor.

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.