Advances in Therapy for Gout: 2015
The Past, Present, and Future

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Therapy for Gout: The Past

The New York Times
May 22, 1997

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.

Famous Sufferers of Gout

Henry VIII
Benjamin Franklin

Dialogue Between Franklin and the Gout
Benjamin Franklin (1780)

FRANKLIN. Eh! Oi! Eh! What have I done to merit these cruel sufferings?

GOUT. Many things; you have ate and drank too freely, and too much indulged those legs of yours in their indolence.

FRANKLIN. Who is it that accuses me?

GOUT. It is I, even I, the Gout.
Gout is an Ancient Disease: Hippocratic Aphorisms c. 400 BCE

Section VI

- 28. Eunuchs do not take the gout, nor become bald.
- 29. A woman does not take the gout, unless her menses be stopped.
- 30. A young man does not take the gout until he indulges in coition.

“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 is becoming interesting again...

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 a UA concentration of 6.8, below the upper limit of “normal” 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 – not diagnostic however!!!!

Case I

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

Acute Gout: Traditional Therapy

- **Acute gout is distinguished from chronic gout**
  - Self limited: Patient returns to normal during an asymptomatic inter-critical period that can last months or years
- **Therapy is aimed at reducing the severity and duration of symptoms and reaching the “inter-critical period” sooner**
- **NSAIDs**
  - Effective and rapid relief of symptoms
  - Contraindicated in patients with GI, Renal, or hypersensitivity concerns
- **Corticosteroids**
  - Intraarticular
  - Systemic
- **Colchicine:**
  - Low dose only (0.6 mg BID)! Not every hour until patient gets sick
  - Likely not as effective as either NSAIDs or corticosteroids
- **Uric Acid lowering therapy is now an option for some during acute flare**
Colchicine for Acute Gout – What’s the real story?

- Colchicine’s use in acute gout dates back decades (even centuries) — Dates back before the establishment of the FDA and its approval process
- Thought to inhibit microtubule formation, thereby blocking leukocyte migration into an inflamed joint
- Classically prescribed only within first 48 hours of symptoms (limits its use)
- Classically prescribed as repeating doses roughly every 2 hours until the patient develops GI toxicity or begins feeling better
- This type of therapy generally felt to be dangerous (especially in patients with renal insufficiency), inhumane, and unacceptable

2006 FDA Initiative: Drugs in use before creation of FDA

- Drugs in use prior to FDA approval process should be “encouraged” to be formally evaluated for safety, purity, and efficacy
- Companies receiving formal FDA approval for “old” medications rewarded with exclusivity in manufacturing, marketing, & distribution
- 2009: multiple manufacturers of generic colchicine at a cost of $0.10/pill

Colchicine Exclusivity

- 2010: URL pharma, a manufacturer of generic colchicine, submitted pharmacokinetic data and results from a small clinical trial using its version of colchicine to treat acute gout.
- Cost of trial(s) est. $55 million. Cost of FDA application est. $45 million.
- FDA approved URL pharma’s version of colchicine, granted it a 3 year exclusivity to market it for gout, and ordered all other generic manufacturers to cease and desist
- Generic colchicine renamed “Colcrys” and price raised from $0.10 to $5/pill. Monthly prescription ($6 to $300). (Could be worth $30 billion/17 years)

$$The Value of Colchicine$$

Takeda of Japan Buys URL Pharma for $800 Million

MARK SCOTT
The Takeda Pharmaceutical Company of Japan agreed on Wednesday to buy URL Pharma for $800 million, plus potential further payments based on the company’s performance.

Takeda to Sell Non-Colcrys URL Pharma, Inc. Generic Business to Sun Pharmaceutical
Dec. 18, 2012 – Takeda Pharmaceutical Company Limited (Takeda) announced today that Takeda’s wholly-owned subsidiary, Takeda Pharmaceuticals U.S.A., Inc. (TPUSA) has entered into a definitive agreement with Caraco Pharmaceutical Laboratories, Ltd. (Caraco), a wholly-owned subsidiary of Sun Pharmaceutical Industries, Ltd. for the sale of the non-Colcrys (colchicine, USP) URL Pharma, Inc.* generic business. With the acquisition of URL Pharma earlier this year, Takeda has become a leader in gout therapy by adding Colcrys to its portfolio. Net sales for Colcrys totalled $155 million from June 1 to September 30, 2012.
The Clinical Value of Colchicine for Acute Gout

- FDA approval based upon one study
  - Examined “Colcrys” in acute gout
  - “High dose” vs “low dose” (0.6 mg BID) vs. placebo
  - No comparison to NSAIDs or Prednisone
  - High dose more toxic and no better than low dose
  - FDA approved “low dose” only
  - While statistically significant response, underwhelming compared to experience with other acute gout treatments

Colchicine for Acute Gout: Summary

- High dose colchicine should NEVER be used to treat any patient with acute gout
  - “Colcrys” brand colchicine is the only FDA approved and available form of colchicine. Although its marketing exclusivity ran out last year, patent awarded for treatment and prophylaxis of acute gout until 2/2029!
  - When dosed as approved (low dose/BID), the efficacy of “Colcrys” for acute gout is underwhelming
  - There are much better regimens at one’s disposal, including NSAIDs and/or Prednisone

Colchicine: How Effective for Acute Gout??

Table 2: Efficacy analysis (inten-to-treat population, n = 184)^

<table>
<thead>
<tr>
<th>Colchicine dose</th>
<th>High (n = 52)</th>
<th>Low (n = 76)</th>
<th>Placebo (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td>17 (33.7) 28 (37.8) 9 (16.7)</td>
<td>19 (32.9) 31 (41.1) 10 (17.4)</td>
<td>16 (29.8) 28 (43.6) 10 (17.8)</td>
</tr>
<tr>
<td>Treatment response based on target joint pain score 24 hours after the first dose</td>
<td>19 (36.5) 31 (41.0) 10 (17.2)</td>
<td>18 (28.3) 32 (45.8) 10 (17.2)</td>
<td>20 (38.5) 34 (45.9) 10 (17.2)</td>
</tr>
</tbody>
</table>

No matter how “response” defined, only about 40% of patients achieve primary endpoint!

Chronic Gout - Progression

- Recurrent inflammatory arthritic attacks separated by diminishing inter-critical periods of normalcy
  - Monoarticular
    - Same joint
    - Spread to other joints
    - General tendency to spread from distal (podagra) to proximal
  - Polyarticular
    - Chronic inflammation/synovitis with no inter-critical period
      - Recurrent attacks blend together and patient’s symptoms never return entirely to normal between attacks
      - Eventually, chronic inflammation remains
    - Tophaceous gout:
      - Can occur with all of the above
      - Uric acid containing tophi deposit in joints/tendons/soft tissues, can lead to erosions and deformities
      - Chronic synovitis and tophaceous deformities can be difficult to distinguish from other inflammatory arthritis such as RA
Managing Chronic Gout: 2012 ACR Guidelines

Chronic Gout – Traditional Management

- **Goal:** Treat to target uric acid level
  - Lower serum uric acid levels are associated with fewer attacks
  - Target serum urate levels below crystallization concentration (<6.0 or even 5.0 if possible) 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 when initiating or adjusting uric acid lowering therapy
  - Colchicine does work well for this (unfortunately, it now costs $5/pill)
  - NSAIDs and prednisone work as well

Treating Hyperuricemia: General principles

- Do not treat asymptomatic hyperuricemia
  - Perhaps someday this will change if primary hyperuricemia is individually linked to cardiovascular or metabolic syndromes
- General goal is:
  - To reduce frequency and severity of subsequent attacks of gout
  - To resorb tophacous uric acid deposits that can cause joint damage
- Allopurinol and febuxostat are considered first-line therapies for hyperuricemia associated with gout
- It's now considered acceptable to initiate urate-lowering therapy during acute flares provided adequate treatment of flare is begun and prophylaxis against future flares is maintained for at least three months after flare

Addressing co-morbid conditions in gout patients with hyperuricemia

<table>
<thead>
<tr>
<th>Table 2: Specific recommendations of a comorbidity checklist for gout patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Appropriate to consider in the clinical evaluation, and if clinically indicated, to evaluate evidence for all:</strong></td>
</tr>
<tr>
<td>Obesity, dietary factors</td>
</tr>
<tr>
<td>Excessive alcohol intake</td>
</tr>
<tr>
<td>Metabolic syndrome, type 2 diabetes mellitus</td>
</tr>
<tr>
<td>Hypertension*</td>
</tr>
<tr>
<td>Hyperlipidemia, modifiable risk factors for coronary artery disease or stroke</td>
</tr>
<tr>
<td>Serum urate lowering medications</td>
</tr>
<tr>
<td>History of urolithiasis</td>
</tr>
<tr>
<td>Chronic kidney disease, or interstitial renal disease</td>
</tr>
<tr>
<td>In selected cases, potential or acquired cause of acid aricular overproduction (e.g., iatrogenic increase in parathyroid hormone or parathyroid hormone), myeloproliferative, or lymphoproliferative disease, respectively)</td>
</tr>
<tr>
<td>Load injection</td>
</tr>
</tbody>
</table>

*Load injection should be considered in the clinical evaluation, and if clinically indicated, to evaluate evidence for all.
Non-pharmacologic treatments for 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

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

Diet recommendations: Fairly Meager evidence

<table>
<thead>
<tr>
<th>Acids</th>
<th>Limit</th>
<th>Encourage</th>
</tr>
</thead>
<tbody>
<tr>
<td>SERVING SUGAR-CONTAINING FOODS</td>
<td></td>
<td></td>
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<tr>
<td>+ Moderate/High-alcohol beverages</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>+ Moderate/High-sodium beverages</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>+ Moderate/High-fat beverages</td>
<td>C</td>
<td></td>
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<tr>
<td>+ Moderate/High-sodium beverages</td>
<td>C</td>
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<tr>
<td>+ Moderate/High-sodium beverages</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>

Khanna et al. Arth Care and Research 2012: 64;10 1431-1446

Allopurinol is purine derivative: a dead ringer for hypoxanthine

Allopurinol competes with Hypoxanthine for xanthine oxidase
Purine Metabolism

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.

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
  - The Role of HLA B5801 and Allopurinol Hypersensitivity is unquestioned
- All patients from populations with a high allele frequency for HLA B5801 and Allopurinol Hypersensitivity should be screened!!

HLA B5801 and Allopurinol Hypersensitivity

Hung et al. PNAS 2005

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Allergic-SCAR</th>
<th>Tolerant control</th>
<th>General population control</th>
<th>Odds ratio</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA B5801</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cw*1502</td>
<td>48 (14.1)</td>
<td>40 (13)</td>
<td>36 (12.3)</td>
<td>1.4 x 10^-3</td>
<td>0.006</td>
</tr>
<tr>
<td>A2*1602</td>
<td>16 (4.5)</td>
<td>14 (4.8)</td>
<td>12 (3.9)</td>
<td>1.1 x 10^-2</td>
<td>0.004</td>
</tr>
<tr>
<td>B40*0101</td>
<td>13 (3.7)</td>
<td>12 (4)</td>
<td>10 (3.3)</td>
<td>1.4 x 10^-2</td>
<td>0.002</td>
</tr>
<tr>
<td>B5801*01</td>
<td>32 (9.1)</td>
<td>27 (9)</td>
<td>25 (8.1)</td>
<td>1.3 x 10^-2</td>
<td>0.002</td>
</tr>
</tbody>
</table>

1. B5801 confers nearly 600 fold increased risk of allopurinol hypersensitivity
2. Allele and association is particularly important in Han Chinese patients, Thai, and Korean patients
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!!

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

You face two problems:

- What to do to treat his symptoms acutely?
- How to manage his now chronic arthropathy in the longer-term?
Managing the Chronic Disease

Once his acute symptoms have improved and he has been adequately prophylaxed against further exacerbations, you now decide to treat his chronic symptoms of gout by:

A. Starting allopurinol 300/day
B. Colchicine 0.6 mg/day
C. Probenecid 250 mg twice daily
D. None of the above

Management of Chronic Gout in a Challenging Patient

You decide to start allopurinol therapy carefully, by beginning with 100 mg QoD and progressing over SEVERAL months to as much as 300 mg QOD. However, the patient develops a fever, rash, and elevated LFTs thought secondary to allopurinol hypersensitivity that necessitates discontinuing the medication. The patient recovers fully and now has a uric acid level of 9.1. His chronic destructive arthritis continues unabated.

Your next Best Step is...

A. To try allopurinol desensitization
B. Ban him from eating all foods with purines
C. Give up
D. Hope that Big Pharma will have an answer.....

Febuxostat (FDA approved 2009)

- First treatment in 40 years in chronic management of 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

Comparison of Febuxostat to Allopurinol

Becker et al. NEJM 2005

- 80mg and 120 mg of fubuxostat superior to allopurinol 300mg/day
  - Percent of patients achieving uric acid <6
  - Greater reduction in serum uric acid levels
- Used in patients with mild-moderate renal insufficiency (SCr ≤1.5 in this study)
- “Safe” for patients with allopurinol reactions
- Note: Allopurinol 300/day is probably suboptimal dose for many patients

<table>
<thead>
<tr>
<th>Table 3: Primary and Secondary End Points</th>
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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)

Febuxostat: Summary

- Cannot be used concomitantly with purine based medicines that are metabolized by xanthine oxidase (leads to toxic levels of 6MP, for example)

- Use should be reserved for those not controlled by or who have a contraindication to maximal allopurinol therapy

Severe Tophaceous Gout:

What if…..

- You could convert relatively insoluble uric acid to a more soluble and excretable metabolite?

- You could achieve a sustained reduction in uric acid levels below 5?

- You were a pig? (Pigs don’t get gout)

- You could reverse-engineer evolution?

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) posses uricase, but not humans have lost gene function
- Rasburicase: a drug derived from aspergillis 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**

- Urinary Excretion

**Efficacy of Pegloticase**

- 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
Efficacy of Pegloticase
Phase 2 (12 week) open label dosing trial 41 patients

Visible Results

Pegloti – CASE
Baraf et al. A&R 2008

• 70-year-old man with a 25-year history of gout
• Urate level of 9.2 mg/dl
• 20 gout flares in the 12 months
• Visible tophi on both hands.
• History of nephrolithiasis, renal insufficiency, hypercholesterolemia
• Patient received six q2 wk. infusions of pegloticase

• 24 hours after first infusion, his urate level decreased to <0.1 mg/dl and remained at <0.1 mg/dl until 2 weeks after the final infusion.

Pegloticase: Not holy grail

• Adverse events:
  – Infusion reactions (not human, even with PEG)
  – Anaphylaxis
  – 80% patients had gout flares despite prophylaxis
  – Contraindicated in G6PD deficient patients
  – May exacerbate CHF
Pegloticase: Not holy grail

- 2 Randomized double blind 6 month FDA approval trials (212 patients, 71% with tophi):
  - 38-47% of patients on 8 mg q2 wks reached primary endpoint (UA<6 80% time at months 3&6) compared to 0% placebo
  - 45% of patients “complete” resolution of at least one tophus without progression or formation of other tophi
    - 81% of responders who reached endpoint had tophus resolution
  - Many patients develop antibodies to drug that increases its clearance and affects its efficacy

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!!

Gout Therapy: The Future

- 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
    - Clear overproduction syndrome

Chronic Gout: Uric Acid Lowering Therapies
Hyperuricemia

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

You face two problems:

- What to do to treat his symptoms acutely?
- How to manage his now chronic arthropathy in the longer-term?
### 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

<table>
<thead>
<tr>
<th>Therapy for Acute Gout: A “Biologic” Future??</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target #2: The Inflammasome</strong></td>
</tr>
<tr>
<td>Gout pathogenesis:</td>
</tr>
<tr>
<td>– Super saturated serum levels of uric acid lead to crystal formation and deposits in joints</td>
</tr>
<tr>
<td>– Crystals are engulfed by macrophages</td>
</tr>
<tr>
<td>– Macrophages release inflammatory cytokines</td>
</tr>
<tr>
<td>– Recruit more inflammatory cells and perpetuate joint inflammation</td>
</tr>
</tbody>
</table>

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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??

### 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
IL-1 Production

• Pro-IL 1 is inactive, but capable of being rapidly metabolized to active IL-1

• Machinery that cleaves pro IL-1 to active IL-1 is called the inflammasome and is induced by a second required danger signal

• Uric Acid is capable of activating the inflammasome

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
So et al. A&R 2010

- 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
So et al. A&R 2010

Secondary endpoints:
- 8 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

Not Quite Ready for Prime Time

FDA rejects expanded use of Regeneron drug for gout
Published July 31, 2012 Reuters
Regeneron Pharmaceuticals Inc said U.S. regulators have denied approval for it to expand use of its Arcalyst 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.

FDA Panel Votes Against Gout Drug
By THOMAS M. BURTON
WASHINGTON—The Food and Drug Administration is grappling with the novel question of whether a Novartis AG NVS +0.97% gout-pain drug should be marketed when patients receiving just one injection had a higher rate of serious infections in clinical studies. An FDA advisory committee Tuesday voted 11-1 against approving the drug, called Ilaris, because of the safety concerns.

Advances in Therapies for Gout: Summary

- Gout is an ancient disease for whom modern therapy is finally available
  - Well managed by internists and PCPs who use standard therapy appropriately for acute vs. chronic gout
- New therapies are available
  - Febuxostat (allopurinol refractory, intolerant, or contraindicated)
  - Pegylated uricase: severe tophaceous disease
  - IL-1 blocking biologic therapy for the most severe disease
- Rheumatology referral appropriate for difficult to manage cases
The future is bright for those with gout who do not go extinct

How does uric acid lead to inflammation???

• The “adaptive” immune system distinguishes self from non-self in highly antigen-specific manner
  – Takes time to mount a naïve antigen-specific response to a specific microbial infection
  – For ex., vaccines can take weeks to become protective

• Arm of immune system can “innately” distinguish foreign microbial molecules from self
  – Patterns are common to many infections and not antigen/pathogen specific (endotoxin, flagella, etc.)
  – Leads to rapid inflammation (even septic shock) that acts as “speed bump” until adaptive immunity kicks in
  – Jump starts adaptive immune response (the need to add adjuvant to a vaccine)

Toll Like Receptors and Their Ligands

2nd “Danger” signal

• Activation of “pattern” receptors primes inflammatory response but does not activate it
  – Don’t want to become septic to one’s own commensal flora!
  – Production of inactive pro-IL 1β into cytoplasm that must be cleaved to active cytokine

• 2nd signal is required to distinguish pathogen from non-pathogen
  – Infected cells release their own cellular contents (eg, DNA/purines)
  – Uric acid is a danger signal!!!!