Crystalline Arthropathies: Diagnosis and Management

Margarita Fallena
Rheumatology Associates
10/01/2016
Introduction

• Most common form of inflammatory arthritis: 3.9% in the US
• Characterized by deposition of monosodium urate monohydrate (MSU) in synovial fluid and other tissues
• The majority of cases are managed in the primary care or acute care settings

Clinical presentation

• Initially presents as acute episodic arthritis
• In early disease patients are asymptomatic in between episodes
• Chronic phase characterized by persistent arthritis, tophi formation, polyarticular attacks
• Tophi are a pathognomonic feature of gout
• Renal manifestations include urolithiasis and chronic interstitial nephropathy

Associated factors

- Consider causes of hyperuricemia for all gout patients
- If clinically indicated evaluate for agents and disorders that cause uric acid underexcretion or overproduction
  - Disease onset before age 25
  - History of urolithiasis

- Comorbidity checklist:
  - Obesity, dietary factors
  - Excessive alcohol intake
  - Metabolic syndrome
  - Diabetes Mellitus
  - Hypertension
  - Hyperlipidemia
  - Serum urate elevating medications
  - History of urolithiasis
  - Chronic kidney disease
  - Overproduction- genetic or acquired
  - Lead intoxication

Khanna et al. Arthritis care and Research: 2012: 64 (10)
SPECIAL ARTICLE

2015 Gout Classification Criteria

An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative
ACR/EULAR 2015 Gout Classification Criteria

Entry criteria:

• At least one episode of swelling, pain or tenderness in a peripheral joint or bursa

Sufficient criteria:

• MSU crystals in a symptomatic joint or bursa
• Tophi

Neogi T et al. Arthritis and Rheumatology: 2015 (67)
ACR/EULAR 2015 Gout Classification Criteria

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Categories</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pattern of joint/bursa involvement</td>
<td>Ankle or midfoot</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>First metatarsophalangeal joint</td>
<td>2</td>
</tr>
<tr>
<td>Characteristics of symptomatic episodes:</td>
<td>Erythema overlying affected joint</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cant bear touch or pressure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Difficulty walking or can't use the joint</td>
<td></td>
</tr>
<tr>
<td>Time course of episodes:</td>
<td>One characteristic</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Two characteristics</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Three characteristics</td>
<td>3</td>
</tr>
<tr>
<td>Clinical evidence of tophus</td>
<td>Present</td>
<td>4</td>
</tr>
</tbody>
</table>

Neogi T et al. Arthritis and Rheumatology: 2015 (67)
ACR/EULAR 2015 Gout Classification Criteria

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Categories</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum urate</td>
<td>&lt;4 mg/dl</td>
<td>-4</td>
</tr>
<tr>
<td></td>
<td>6-8 mg/dl</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>8-&lt;10 mg/dl</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>&gt;10 mg/dl</td>
<td>4</td>
</tr>
<tr>
<td>Synovial fluid analysis</td>
<td>MSU negative</td>
<td>-2</td>
</tr>
</tbody>
</table>

Neogi T et al. Arthritis and Rheumatology: 2015 (67)
## ACR/EULAR 2015 Gout Classification Criteria

<table>
<thead>
<tr>
<th>Imaging</th>
<th>Categories</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound evidence of double contour sign or DECT demonstrating urate deposition</td>
<td>Present</td>
<td>4</td>
</tr>
<tr>
<td>Imaging evidence of gout related joint damage (at least one erosion)</td>
<td>Present</td>
<td>4</td>
</tr>
</tbody>
</table>

Neogi T et al. Arthritis and Rheumatology: 2015 (67)
Conventional Radiography

Typical radiographic findings:
Well defined, “punched out” erosions with overhanging edges

Neogi T et al. Arthritis and Rheumatology. 2015 (67)
Double contour sign:
Ultrasound of ankle joint with MSU crystal deposition across the top of the talar cartilage

Ther Adv Musculoskelet Dis. 2014 Aug; 6(4): 131–143
Dual Energy CT (DECT)

• Allows the distinction of two materials such as calcium and urate crystals

• The unique chemical composition of uric acid precipitates results in a distinct radiographic attenuation when compared to other materials

Dual-energy CT for the diagnosis of gout: an accuracy and diagnostic yield study

• Accuracy study:
  • Patients presenting to the Mayo Clinic Rheumatology clinic with joint pain and swelling
  • Patients with tophaceous gout were excluded
  • Synovial fluid was aspirated from a symptomatic joint
  • Patients divided in two groups based on SF fluid analysis: gout and controls
  • DECT scan of the aspirated joint performed within 2 weeks of joint aspiration
  • The presence of green coloured voxels in articular or periarticular structures was classified as positive

Dual-energy CT for the diagnosis of gout: an accuracy and diagnostic yield study

• Diagnostic yield study:
  • Patients with clinical presentation consistent with gout with negative synovial fluid or unable to perform aspiration
  • All underwent DECT scan, if positive ultrasound guided aspiration was performed

ACCURACY STUDY RESULTS

119 patients
28 excluded (inadequate samples)

43 diagnosed with gout
40 had DECT done

36 (90%)
Positive scan

4 had negative scans:
All first episode
All <6 weeks symptoms

48 with negative SF
41 had DECT

7 showed MSU:
All with knee OA

34 negative

SENSITIVITY 0.9 AND SPECIFICITY 0.83

Advanced knee osteoarthritis: Negative synovial fluid

Diagnostic study results

- 30 patients with undifferentiated arthritis
- DECT positive in 14/30
- 12 underwent aspiration
  - 11/12 showed crystals

DECT take home points

• Patient selection is key when considering DECT scan
  • Limited sensitivity in acute gout with no prior episodes
  • Limited specificity in knee osteoarthritis
Patients with Gout Treated with Conventional ULT: Association with Disease Control, Health Related Quality of Life and Work Productivity

1204 patients with gout on ULT:
- 69.4%: inadequate control
- 30.6% adequate control

Wood R et al. J Rheumatol First Release April 2016
Effect of urate-lowering therapy on the risk of cardiovascular disease and all cause mortality in patients with gout

44,447 individuals:
- 2646 with gout
- 55% treated with ULT

Primary outcome:
CVD mortality

Chen et al. J Rheumatol 2015;42:1694-701
Silent Monosodium Urate Crystal Deposits Are Associated With Severe Coronary Calcification in Asymptomatic Hyperuricemia

• 25% of patients with asymptomatic hyperuricemia have silent articular MSU crystal deposits
• Crystal deposition precedes clinical gout
• Objective: to determine whether coronary artery disease is more severe in patients with asymptomatic hyperuricemia (AH) with crystal deposition compared with patients with AH alone and those with normal uric acid levels
• Observational, prospective association study

Silent Monosodium Urate Crystal Deposits Are Associated With Severe Coronary Calcification in Asymptomatic Hyperuricemia

- Patients admitted due to unstable angina or non ST elevation MI
- Uric acid level >7
- Ultrasound of the knees and first MTP joint-if changes consistent with MSU deposition seen the patient underwent joint aspiration
- Severity of CAD evaluated by coronary angiography

Silent Monosodium Urate Crystal Deposits Are Associated With Severe Coronary Calcification in Asymptomatic Hyperuricemia

Frequency of moderate to severe coronary calcification in patients with normouricemia, asymptomatic hyperuricemia without crystals and AH patients with MSU crystals

2012 American College of Rheumatology Guidelines for Management of Gout. Part 1: Systematic Nonpharmacologic and Pharmacologic Therapeutic Approaches to Hyperuricemia
General dietary measures for gout patients

<table>
<thead>
<tr>
<th>Avoid</th>
<th>Limit</th>
<th>Encourage</th>
</tr>
</thead>
</table>
| Organ meats high in purine content (liver, kidney)  | Serving sizes of: beef, lamb, pork  
Seafood with high purine content: sardines, shellfish | Low fat or non fat dairy products        |
| High fructose corn syrup sweetened sodas, other beverages or foods | Servings of naturally sweet fruit juices  
Table sugar, desserts  
Salt |  |
| Alcohol overuse (>2/day for male, >1/day female)  
Any alcohol use during symptomatic periods | Alcohol (particularly beer but also wine and spirits) |  |

Khanna et al. Arthritis care and Research: 2012: 64 (10)
Baseline recommendations for patients with diagnosis of gout:

- Patient education, diet and lifestyle recommendations
- Consider secondary causes of hyperuricemia
- Consider elimination of non essential medications
- Clinically evaluate disease burden

Indications for pharmacologic urate lowering therapy:

- Tophus or tophi by physical exam or imaging study
- Frequent attacks of acute gouty arthritis (>2/year)
- CKD stage 2 or worse
- Past urolithiasis

Khanna et al. Arthritis care and Research: 2012: 64 (10)
The minimum serum urate target is <6 mg/dL
- Serum urate lowering below 5mg/dL may be needed

**Treat to serum uric acid level:**

- Select first line ULT agent:
  - Allopurinol
  - Febuxostat
  - Alternative: Probenecid

**Acute gout prophylaxis**

- **Treat to target:**
  - Serum uric acid achieved?

- **No:**
  - Increase intensity of ULT

Khanna et al. Arthritis care and Research: 2012: 64 (10)
Long term management of gout

- Continue gout attack prophylaxis if ongoing symptoms or tophi
- Monitor serum urate and medication side effects
- After all tophi and symptoms have resolved continue medications to maintain uric acid <6 indefinitely

Khanna et al. Arthritis care and Research: 2012: 64 (10)
Xantine oxidase inhibitors:
- Block the synthesis of uric acid

Uricase:
- Converts uric acid into soluble allantoin

Uricosuric agents:
- Enhance uric acid excretion
- Inhibit urate reabsorption by proximal renal tubule epithelial cells

Allopurinol

• Starting dose no greater than 100 mg/day or 50 mg/day if stage 4 CKD
• Gradually increase dose every 2-5 weeks to SUA target
• Dose can be >300 mg even with CKD if has appropriate monitoring and education
• Consider HLA-B*5801 testing if appropriate

Khanna et al. Arthritis care and Research: 2012: 64 (10)
Allopurinol side effects

• Mild hypersensitivity with maculopapular eruption
• Severe cutaneous adverse reactions: incidence 0.69 per 1000 person years.
  • Stevens Johnson syndrome/ toxic epidermal necrolysis
  • Drug reaction with eosinophilia and systemic symptoms (DRESS)
  • Allopurinol hypersensitivity syndrome:
    • Rash, eosinophilia, leukocytosis, fever, hepatitis and progressive kidney failure
    • Mortality ranges from 9 % to 20%

Stamp et al. Nature Reviews Rheumatology. 2016 (12)
### Diagnostic criteria for Allopurinol Hypersensitivity Syndrome

| A clear history of exposure to allopurinol |
| Lack of exposure to other drug which may have caused a similar clinical picture |
| A clinical picture including: |
| 1. At least two of the following major criteria: |
|   • Worsening renal function |
|   • Acute hepatocellular injury |
|   • Rash, including toxic epidermal necrolysis, erythema multiforme, or a diffuse maculopapular or exfoliative dermatitis |

**OR**

| 2. One of the major criteria plus at least one of the following minor criteria: |
|   • Fever |
|   • Eosinophilia |
|   • Leukocytosis |

AHS: Genetic Factors

• HLA-B is a member of the family of HLA genes
• HLA-B*5801:
  • Associated with increased risk of AHS
• Recommended testing:
  • Korean descent with stage 3 or worse CKD (allele frequency -12%)
  • Han Chinese or Thai irrespective of renal function (6-8%)
• If positive: prescribe alternative to allopurinol

Khanna et al. Arthritis care and Research: 2012: 64 (10)
AHS: Time Related Factors

1,080 days

Stamp LK et al. Arthritis and Rheumatism:2012 (64)
# AHS: Drug Related Factors

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=53)</th>
<th>Controls (n=152)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol starting dose higher than the creatinine clearance based dose</td>
<td>23 (43.4%)</td>
<td>18 (11.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Allopurinol starting dose the same as or lower than the creatinine clearance based dose</td>
<td>30 (56.6%)</td>
<td>134 (88.2%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Drug concentration:**
- Dose
- Renal failure
- Diuretic use

Stamp LK et al. Arthritis and Rheumatism: 2012 (64)
Minimizing AHS risk

• Use allopurinol only when clearly indicated
• Consider alternate urate lowering therapy if multiple risk factors are present
• Educate patients about early symptoms of adverse reactions including pruritus, fever and rash and recommend to promptly stop therapy
• Order genetic screening when indicated
• Follow guidelines on starting dose
• Modify/stop non essential medications if possible
Recommendations specific to primary uricosuric lowering therapy

• Probenecid is the first choice
• Not recommended if creatinine clearance less than 50 ml/minute
• Fenofibrate and losartan can be used as components of a comprehensive urate lowering therapy strategy
• Measure urinary uric acid before starting therapy
Probenecid

• Contraindicated in:
• History of urolithiasis
• Elevated urine uric acid-indicative of uric acid overproduction
• Consider urine alkalination with monitoring of urine pH in addition to increased fluid intake

Khanna et al. Arthritis care and Research: 2012: 64 (10)
Lesinurad

- Approved by the FDA in December 2015 based on the results of 3 phase III trials (CLEAR1, CLEAR2 and CRYSTAL)
- Indication: hyperuricemia associated with gout in patients who have not achieved target serum uric acid (sUA) levels with a xanthine oxidase inhibitor alone
- Selective uric acid reabsorption inhibitor (SURI) that inhibits the URAT1 transporter responsible for the majority of the reabsorption of uric acid from the renal tubular lumen
- Should be used in combination with allopurinol or febuxostat
- Side effects include gout flares and elevated creatinine levels

Lesinurad, a Novel Selective Uric Acid Reabsorption Inhibitor, in Two Phase III Clinical Trials: Combination Study of Lesinurad in Allopurinol Standard of Care Inadequate Responders

- Two replicate studies (CLEAR 1, CLEAR 2)
- Lesinurad (200 mg or 400 mg) in combination with allopurinol vs allopurinol + placebo
- Serum uric acid (sUA) ≥6.5 mg/dL
- ≥2 gout flares in the prior 12 months
- Primary endpoint was the proportion of subjects meeting sUA target of <6.0 mg/dL by Month 6

Saag et al. ACR meeting abstract 2014
Figure.

CLEAR 1 and CLEAR 2 Primary Endpoint
% subjects achieving sUA of <6 mg/dL at Month 6
ITT population, non-responder imputation

LESU200 VS PBO (CLEAR 1 and 2 combined): RR = 2.15, 95%CI: 1.78, 2.59
LESU400 VS PBO (CLEAR 1 and 2 combined): RR = 2.46, 95%CI: 2.05, 2.95

# P < 0.0001 vs. PBO + ALLO arm.
NOTE: Relative risks are post-hoc calculations, not adjusted for randomization stratification factors.
ALLO: allopurinol; LESU200: lesinurad 200 mg; LESU400: lesinurad 400 mg; PBO: placebo;
ITT: intent-to-treat; CI: confidence interval; RR: relative risk.
Recommendations for refractory disease

- Upward dose titration of one xanthine oxidase inhibitor to the maximum appropriate dose
- Substitution of febuxostat for allopurinol or vice versa
- Addition of a uricosuric agent to a xanthine oxidase inhibitor or vice versa
- Consider using pegloticase in severe or refractory disease or patients who are intolerant to conventional therapy
  - Not recommended as first line therapy for any case scenario
  - Lack of consensus on therapy duration

Khanna et al. Arthritis care and Research: 2012: 64 (10)
Pegloticase use in refractory or severe disease

- ULT fails in 3% of patients because of contraindication, refractoriness or intolerance
- Two randomized, 6 month, double blind trials
- Patients with refractory gout:
  - Uric acid level >8 mg/dL
  - At least one of the following:
    - 3 or more flares in the past 18 months
    - Gouty arthropathy: joint damage due to gout
    - 1 or more tophi
  - Allopurinol contraindicated or failed

Sundy J et al. JAMA 2011: 306 (7)
Pegloticase use in refractory or severe disease

• 225 patients randomized to 3 study groups:
  • Biweekly pegloticase
  • Monthly pegloticase
  • Placebo

• Responder= Plasma uric acid <6 for >80% of the time during months 3 and 6

<table>
<thead>
<tr>
<th># Responders/ # Treated</th>
<th>Biweekly</th>
<th>Monthly</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>36/85 (42%)</td>
<td>29/84 (35%)</td>
<td>0/43 (0%)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

Sundy J et al. JAMA 2011: 306 (7)
Pegloticase use in refractory or severe disease

• Secondary end points:
  • 40%/21% resolution of 1 or more tophi compared to 7% in the placebo group (P=.002/.20)
  • During months 1-3 increased number of gout flares in the treated groups
  • During months 4-6 significant reduction in gout flares in the biweekly vs. placebo group
  • Significant improvement in physical function and reduced pain in the biweekly group

• Adverse events:
  • Gout flare
  • Infusion related reaction
    • Antibodies present in 134 of 150 (89.3%) patients
    • Patients with higher antibody titers had less response to treatment and more likely to have infusion reactions

Sundy J et al. JAMA 2011: 306 (7)
ACR GUIDELINES PART 2: THERAPY AND ANTIINFLAMMATORY PROPHYLAXIS OF ACUTE GOUTY ARTHRITIS

Assess severity

Monotherapy

NSAID or Cox-2 inhibitor

Systemic steroids

Colchicine

Start treatment within 24 hours of onset

Do not interrupt ongoing ULT

Successful outcome: Patient education
Initiate or adjust ULT

Khanna D et al. Arthritis Care and Research: 2012 (64)
<table>
<thead>
<tr>
<th>NSAIDs</th>
<th>Colchicine</th>
<th>Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>No specific NSAID as first line treatment</td>
<td>Use when onset not greater than 36 hours</td>
<td>1-2 joints: oral or intra articular steroids</td>
</tr>
<tr>
<td>FDA approved: Naproxen, indomethacin and sulindac</td>
<td>Loading dose 1.2 mg followed by 0.6 mg one hour later</td>
<td>Prednisone 0.5 mg/kg per day for 5-10 days or 2-5 days at the full dose followed by 7-10 day taper</td>
</tr>
<tr>
<td>Continue until symptoms fully resolved</td>
<td>Then 0.6 mg twice a day until symptoms resolve</td>
<td>Other acceptable options: Methylprednisolone dose pack 60 mg intramuscular triamcinolone followed by oral steroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Khanna D et al. Arthritis Care and Research: 2012 (64)</td>
</tr>
</tbody>
</table>
Severe pain, polyarticular attack

Multiple large joints

Alternate monotherapy

Add-on combination therapy:
- Colchicine + NSAIDs
- Systemic steroids and colchicine
- Intraarticular steroids + NSAIDs or colchicine

Inadequate response

Off label therapies

Interleukin-1 inhibition

Inadequate response

Khanna D et al. Arthritis Care and Research: 2012 (64)
MECHANISMS OF INFLAMMATION AND IL-1 ANTAGONISM IN ACUTE GOUT

IL-1 As a Therapeutic Agent in Gout

- IL-1β is a potent pro-inflammatory cytokine
- IL-1 blockade has been shown to effectively:
  - Treat acute gouty arthritis
  - Prevent gout flares when starting uric acid therapy

<table>
<thead>
<tr>
<th>Name</th>
<th>Mechanism of action</th>
<th>Half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anakinra</td>
<td>IL-1 receptor antagonist</td>
<td>4-6 hours</td>
</tr>
<tr>
<td>Rilonacept</td>
<td>Fusion protein (binds IL-1α and β)</td>
<td>7-9 days</td>
</tr>
<tr>
<td>Canakinumab</td>
<td>Human anti-IL1β monoclonal antibody</td>
<td>26 days</td>
</tr>
</tbody>
</table>

Dumusc et al. Curr Opin Rheumatol. 2015 (27) 156-163
Anakinra for acute gouty arthritis

• No randomized controlled trials
  • 2007: open labelled proof of concept study 10 patients 100 mg SQ x 3 days reported rapid clinical response
  • 2010 Chen et al. retrospective study of 10 patients: 6/10 good response, 3/10 partial response, 1 patient did not respond
  • 2013 Ottaviani et al: retrospective study of 40 patients: 90% good response

• Prospective, randomized studies needed

• With short half life: potential short term use in hospitalized patients with comorbidities or contraindication to other medications

Dumusc et al. Curr Opin Rheumatol. 2015 (27) 156-163
Rilonacept

• For acute gouty arthritis:
  • Terkeltaub et al (2013): Randomized, placebo controlled trial (phase 3) rilonacept single injection vs. indomethacin in 225 patients
  • Rilonacept in combination with indomethacin and rilonacept alone did not provide additional pain relief over 72 hours relative to indomethacin alone

• Acute gout flare prevention:
  • 3 randomized controlled trials have evaluated prevention of acute flares during initiation of ULT
  • All studies showed good efficacy compared to placebo

Dumusc et al. Curr Opin Rheumatol. 2015 (27) 156-163
Canakinumab

• Approved in Europe for patients with frequent gouty attacks (>3/12 months) since 2013

• At least 3 RCTs, most recent 2012 Schlesinger et al: 456 patients canakinumab 150 mg SQ single injection vs triamcinolone 40 mg IM
  • Mean pain scores at 72 hours lower in the canakinumab group
  • Patient self global assessment, tenderness, swelling and erythema also significantly lower
  • More adverse events including serious infections in the canakinumab group
  • Debate over 40 mg vs 60 mg dose of triamcinolone

• For gout flare prevention one RCT in 2011: patients on allopurinol, compared canakinumab to colchicine
  • Showed reduction in the mean number of flares, time to first new gout flare was longer and duration of flare was shorter in the canakinumab group

Dumusc et al. Curr Opin Rheumatol. 2015 (27) 156-163
Recommendations for NPO patients

• 1-2 large joints: intraarticular steroids
• Intravenous or intramuscular methylprednisolone 0.5-2 mg/kg
• Subcutaneous ACTH 25-40 IU with repeat doses as indicated

Khanna D et al. Arthritis Care and Research: 2012 (64)
RECOMMENDATIONS FOR PHARMACOLOGIC ANTIINFLAMMATORY PROPHYLAXIS OF ATTACKS OF ACUTE GOUT

For all patients where ULT is initiated

First line therapy:
Colchicine OR Low dose NSAID with PPI

Intolerant or contraindicated

Low dose prednisone <10 mg

For how long?

At least 6 months or

3 months after achieving target uric acid (if no tophi)

6 months after achieving target uric acid if tophi present

Khanna D et al. Arthritis Care and Research: 2012 (64)
Limited literature on surgical treatment, no controlled trials

Based on available literature recommendation is to reserve surgery for patients with severe, debilitating disease with complications in the following settings:

- Refractory disease despite maximal medical therapy
- Poorly controlled pain attributable to a tophus
- Nerve compression or entrapment
- Uncontrolled or recurrent infection
- Discharging sinus
- Significant skin ulceration
- Function impairment
- Joint instability and impaired joint motion preventing patient from working or limiting daily activities

Cosmetic surgery should be considered only after failing medical therapy
