Gout: What’s Out

Mikaela DeBarba, Pharm.D.
PGY1 Community Pharmacy Resident
H-E-B Pharmacy/University of Texas at Austin
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mikela.farrell@utexas.edu

Objectives

- Define gout and review epidemiology
- Review guidelines for gout
- Review literature on monitoring serum urate level while on uric lowering therapy
- Formulate a recommendation for monitoring serum uric acid levels

Case

You are working on an MTM case. The patient is a 45 year old male who suffers from chronic gout. He has been on allopurinol 100 mg daily for 6 weeks. He has not had any flares and his serum urate level has not been checked.

- Do you recommend lab testing to the doctor and patient?

Gout

- **Gout**: most common form of inflammatory arthritis caused by accumulation of excess urate crystals (monosodium urate, MSU) in joint fluid, cartilage, bones, tendons, bursas, and other sites
- **Tophus**: hard, MSU deposits under the skin

Epidemiology

- $1$ billion annually on ambulatory care for gout
- $60\%$ of people with initial flare experience a second flare within $1$ year and $78\%$ do so within $2$ years

Serum Urate Level (SUA)

- Hyperuricemia is when urate concentration exceeds the limit of urate solubility in serum (approximately $6.8$ mg/dl)
- Hyperuricemia is the main cause of flares, tophi, and joint damage

Question 1

True or False:

A $45$ year old male with a SUA of $8$ mg/dl is more likely to have a gout attack than a $50$ year old female with the same SUA level.

**TRUE**

Men are $3$-$4$ times more likely to experience a gout attack than women.
Medications for gout attacks

**Anti-inflammatory**

- **NSAIDs**
  - MOA: Non-selective inhibitors of COX 1 & 2 which reduces the synthesis of prostaglandins that are involved in mediating inflammatory responses

- **Colchicine**
  - MOA: Binds to microtubular protein in neutrophils, inhibiting both their chemotactic and chemokinetic responses. Inhibits leukotriene B4 formation and inhibits release of histamine from mast cells

- **Corticosteroids**
  - MOA: Thought to involve phospholipase A₂ inhibitory proteins which control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of the precursor molecule arachidonic acid.

Medications for chronic gout

**Urate Lowering Therapy (ULT)**

- **Xanthine oxidase inhibitors (XO)**
  - MOA - decrease the synthesis of uric acid from purines
    - **Allopurinol**
      - Purine analog
      - Drug hypersensitivity reactions (eg. Stevens-Johnson & DRESS syndromes)
    - **Febuxostat (Uloric *)**
      - Non-purine selective non-competitive inhibitor of xanthine oxidase

- **Uricosuric**
  - MOA: organic acids that inhibit the reabsorption of uric acid by inhibiting anionic transport sites of the renal proximal tubule
    - **Probenecid**
      - For patients who can’t tolerate allopurinol, or require additional urate lowering

- **Uricoslytic**
  - MOA: converts uric acid to a water soluble metabolite
    - **Pegloticase (Krystexxa *)**
      - Reserved for the treatment of severe, treatment-refractory chronic gout
Question 2
A 67 year old male patient with a history of kidney stones who is on a fixed income is not responding to his allopurinol treatment. What treatment should you put the patient on?

a) Allopurinol
   - Not responding
b) Febuxostat
   - Contraindicated in patients with kidney stones
c) Probenecid
   - Very expensive
d) Pegloticase

B. Febuxostat

Guidelines

- ACR • American College of Rheumatology • 2012
- 3e • Evidence, Expertise, Exchange • 2013
- EULAR • European League Against Rheumatism • 2016

New guidelines

- ACP • American College of Physicians • 2016

Recommendations for target SUA level while on a ULT

- ACR • Maximum of 6 mg/dl
- 3e • <6 mg/dl
- EULAR • <6 mg/dl if tophi are present
- ACP • <5 mg/dl for severe gout

- Evidence is insufficient for monitoring of serum urate levels in patients with gout
Controversy

Gout expert Robert Terkeltaub, MD, president of the Gout, Hyperuricemia and Crystal-Associated Disease Network (G-CAN)

“The guideline compromises gout-specific patient education, imperils good outcomes, and could set optimal treatment of the disease back decades”

Controversy

Gout expert Robert Terkeltaub, MD, president of the Gout, Hyperuricemia and Crystal-Associated Disease Network (G-CAN)

“It would be unfortunate if something as simple as getting uric acid levels done to routinely monitor serum uric acid were to be impacted at the third-party payer level”

Controversy

ACP Vice President for Clinical Policy Amir Qaseem, MD, PhD, MHA

“This threshold (6.8 mg/dl) is not absolute because patients with higher serum urate levels may still be asymptomatic, and some may have acute flares below this threshold. There is an association between lower urate levels and fewer gout flares, the extent to which use of urate-lowering therapy to achieve various targets can reduce gout flares is uncertain.”

Controversy

ACP Vice President for Clinical Policy Amir Qaseem, MD, PhD, MHA

"There is no evidence from an experimental study that examined the health outcomes of treating to one serum uric acid level versus another, nor is there a trial comparing a strategy of basing treatment on attaining a specific urate level versus basing treatment on reduction in symptoms (such as gout flares)."
Question 3

All but ACP guidelines recommends the treat-to-target recommendation. Which drug does this pertain to?

a) Naproxen
b) Colchicine
c) Allopurinol
d) Prednisone

C – Allopurinol

Treat to target recommendation is in regards to how urate lowering therapy is monitored for chronic gout.

Andrés et al. 2014

<table>
<thead>
<tr>
<th>Title</th>
<th>Treatment Target and Follow-up Measures for Patients with Gout: A Systematic Literature Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>Systematically review the validity of serum uric acid (SUA) as a treatment target for patients with gout.</td>
</tr>
</tbody>
</table>
| Design | • Systemic literature review
        • Search performed in Medline, Embase and the Cochrane Library
        • Studies evaluating different SUA levels or SUA reduction with the achievement of outcomes were selected |
| Patients | 54 articles used |
| Statistics | Validity – correlation coefficients and regression analyses |

Andrés et al. 2014

Results

<table>
<thead>
<tr>
<th>6 studies</th>
<th>2 studies</th>
<th>5 studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Found that lower SUA level was significantly associated with fewer gouty attacks</td>
<td>• Addressed the association of SUA level with changes in tophi size</td>
<td>• Evaluated if lowering SUA is associated with clearance of MSU crystals from joints</td>
</tr>
</tbody>
</table>

Andrés et al. 2014

Limitations

• No statistical analysis discussed
• Most current study was 2010

Conclusions

• Evidence supporting reducing SUA level as a treatment target for patients with gout as a surrogate marker
• Cutoff point for SUA level remains unclear
Krishnan et al. 2013

<table>
<thead>
<tr>
<th>Title</th>
<th>Serum urate and incidence of kidney disease among veterans with gout</th>
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</thead>
<tbody>
<tr>
<td>Objective</td>
<td>Study the association between serum urate level (SUA) and the risk of incident kidney disease among US veterans with gouty arthritis.</td>
</tr>
</tbody>
</table>
| Design | Retrospective cohort study
South Central Veterans’ Affairs Health Care Network
January 1, 2002 to January 1, 2011 |
| Patients | 2116 patients ≥ 18 years of age
At least 2 recorded SUA level and enrolled in the database for a minimum of 6 months before and 12 months after the first measurement
Grouped in 2 groups: overall low SUA and high SUA levels |
| Statistics | Accumulated hazard curves for time to event were estimated for both SUA groups and statistical comparison was conducted using a log-ranked test
Multivariate adjusted analysis used a Cox proportional hazard model to estimate the relative risk of kidney disease associated with high vs low SUA |

Results

<table>
<thead>
<tr>
<th>Identification of Patients with Gout</th>
<th>N</th>
<th>Hazard Ratio</th>
<th>Lower 95% Confidence Limit</th>
<th>Upper 95% Confidence Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 2 gout diagnoses</td>
<td>2116</td>
<td>1.43</td>
<td>1.20</td>
<td>1.70</td>
</tr>
<tr>
<td>At least 2 gout diagnoses and at least 1 gout medication</td>
<td>2006</td>
<td>1.44</td>
<td>1.20</td>
<td>1.72</td>
</tr>
<tr>
<td>At least 3 gout diagnoses</td>
<td>1879</td>
<td>1.49</td>
<td>1.24</td>
<td>1.79</td>
</tr>
</tbody>
</table>

Limitations

- Excluded women
- Used >7 mg/dl as the cut-off

Conclusions

- Gout patients with SUA >7 mg/dl developed more kidney disease than gout patients with SUA <7 mg/dl
Sarawate et al. 2006

Title: Serum Urate Levels and Gout Flares
Analysis From Managed Care Data

Objective: Determine the relationship among gout-specific prescription drug therapy, serum urate level (SUA), and gout flares among adult gout patients

Design:
- 2-year, nonrandomized, retrospective, database analysis of patients identified as having gout from a managed care perspective
- Database included medical claims, pharmacy claims, electronic laboratory results, and health plan eligibility
- January 1, 1999 to March 31, 2004

Patients: 5942 gout patients ≥18 years of age
- Differentiated as newly or previously diagnosed

Statistics:
- Multivariable logistic regression and negative binomial regression analyses were conducted to evaluate the association between SUA level ≥6 mg/dl and risk and rate of gout flares, respectively

Results

- Patients with a SUA level ≥6 mg/dl while on urate lowering medication have a greater likelihood of gout flares
- Failure to attain target SUA level and the occurrence of gout flares may have multifactorial origins

Limitations:
- Nonrandomized retrospective study
- SUA results were not available for all patients pre- and postindex

Conclusion:
- Patients with a SUA level ≥6 mg/dl while on urate lowering medication have a greater likelihood of gout flares
- Failure to attain target SUA level and the occurrence of gout flares may have multifactorial origins

Shoji et al. 2004

Title: A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy

Objective: Evaluate the proposed relationship between persistent reduction of serum urate into the subsaturating range and reduction in the frequency of acute gouty attacks

Design:
- Retrospective analysis
- Institute of Rheumatology, Tokyo Women’s Medical University
- January 1, 1997 to June 30, 1998

Patients: 267 patients; 35 received no ULT, 232 received ULT
- Experienced at least 1 attack of gouty arthritis and none were then receiving ULT

Statistics:
- Evaluated the relationship between average serum urate concentration during the whole investigation period and recurrence of gouty attacks by a logistic regression model
- Relationship between ULT and the recurrence of gouty attacks was analysed using a logistic regression model
Shoji et al., 2004

Results

Limitations

- Population is not generalizable
- Attacks in first year were not included

Conclusion

- Demonstrated that the lower the serum urate level, the less the likelihood of recurrent acute gouty attacks
- Mean average serum urate concentration in the patients in the medication group who experienced recurrent gouty attacks was only 7.01 mg/dl which suggests that 7 mg/dl is not a suitable target level

Perez-Ruiz et al., 2002

Title

Effect of Urate-Lowering Therapy on the Velocity of Size Reduction of Tophi in Chronic Gout

Objective

Evaluate the relationship between serum urate level during therapy and the velocity of reduction of tophi in patients with chronic tophaceous gout

Design

- Prospective, observational study
- Gout clinic at a regional reference hospital
- 1995 to 2000

Patients

- 63 patients
- Patients had tophaceous gout and were willing to take ULT with long-term follow-up

Statistics

No analysis
Perez-Ruiz et al, 2002

Results

Limitations

- Small sample size
- Serum urate level during ULT was considered the average of all serum urate measurements during entire follow-up period

Conclusion

- Lower the serum urate level achieved during ULT, the faster the reduction in tophaceous deposits
- All serum urate levels before ULT were ≥ 8.78 ± 1.34 during follow-up were less than 5.37 ± 0.79

Question 4

True or False:
If SUA level is <6 mg/dl a patient will not have a gout flare.

False
Studies have shown patients with any SUA level can have flares

Conclusion

- There is a correlation between the SUA level and gout flares
- The velocity of gouty tophus size reduction was inversely related to serum urate level achieved during urate-lowering therapy
- There are no studies that prove <6 mg/dl is the best target to reduce flares
- Checking SUA level while titrating ULTs are in all guidelines except ACP
Case
You are working on an MTM case. The patient is a 45 year old male who suffers from chronic gout. He has been on allopurinol 100 mg daily for 6 weeks. He has not had any flares and his serum urate level has not been checked.
Do you recommend lab testing to the doctor and patient?

Question

Thank You
• Nathan Pope, Pharm.D., BCACP
• H-E-B/UT Residency Program Preceptors
• Co-residents at H-E-B/UT
• Lucas Hill, Pharm.D.

Resources
**Elevated Purine Source**
- Catabolism of Purines
- Tumor lysis syndrome
- Diet
  - meat (beef, pork, lamb)
  - seafood (scallops, shrimp, tuna)
  - beer, distilled spirits
  - drinks with fructose

**Gout Risk Factors**
- Male gender
- Age
- Obesity
- Ethnicity (Pacific Islanders)
- Polymorphisms (genetics)
- Kidney disease

**Hyperuricemia Related Risks**
- Joint inflammation
- Kidney or bladder stones
- Nephropathy
- CV disease
- Metabolic syndrome

**↑ Purines**

**Xanthine oxidase**

**↑ Urate pool (hyperuricemia)**

**Decreased Renal Clearance** *
- Drugs (HTZ, aspirin...)
- Fructose
- Genetic factors
- Kidney disease

* ~90% of cases of gout are caused by inefficient renal excretion of urate vs. over production.
Krishnan et al. 2013
Results

Sarawate et al. 2006
Results
Shoji et al, 2004
Results

Perez-Ruiz et al, 2002
Results

Figure 1. Mean serum urate levels versus velocity of reduction of tophi. There is a linear relationship between the 2 parameters ($r = -0.62$, $r^2 = 0.48$; $P < 0.05$).