Refractory Gout:
An overview of pathogenesis and treatment

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Disclosures

1. Horizon Pharma, Plc: Research; Speaker Bureau
2. Takeda Pharmaceuticals USA, Inc.: Speaker Bureau; Advisory Board
Objectives

• To review the etiopathogenesis of gout as a chronic, progressive, inflammatory arthritis

• To differentiate the treatment of acute gout flares vs. chronic gouty arthropathy

• To discuss the management of refractory gout

• To facilitate collaboration between podiatrists and rheumatologists in the management of gout patients
Gout definition

- An inflammatory arthritis caused by the deposition of monosodium urate (MSU) crystals in synovial fluid and other tissues
  - Crystal deposition occurs when serum uric acid (SUA) concentration exceeds its solubility
  - As gout progresses, crystal deposition can occur anywhere in the body
  - Chronic disease can lead to sequelae including:
    - Bone erosions
    - Tophi
    - Chronic pain
    - Joint deformities
    - Loss of function
    - Disability

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Calculated Urate Solubility (mg/dL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>37°C (98.6°F)</td>
<td>6.8</td>
</tr>
<tr>
<td>35°C (95.0°F)</td>
<td>6.0</td>
</tr>
<tr>
<td>30°C (86.0°F)</td>
<td>4.5</td>
</tr>
</tbody>
</table>
Gout is a chronic, progressive disease

Acute intermittent gout (flares)

- Crystal deposition
- Low-grade inflammation
- Asymptomatic hyperuricemia
- Acute gout with intercritical periods
- Advanced gout

Subclinical inflammation may be present even in the intercritical periods

Prevalence

- Gout is the most common form of inflammatory arthritis
- Est. prevalence in U.S. 2007-2008: 3.9% (8.3 million)
- Prevalence is increasing worldwide
- Incidence is greater in men than in women
- Incidence increases with age
  - Mainly due to proportional decline in renal function
- Refractory gout estimated to be 2% of all gout patients

Spectrum of Gout

Estimated number of affected persons in the US

8.3 million (3.9%)\(^1\) → 2.6 million → 200-500,000 (1-3%)

Patients with Gout → Treated with Urate-lowering agents → Uncontrolled gout/Refractory Chronic Gout/Refractory to Conventional Therapy

Acute Intermittent Arthritis

Average 10-15 years → Chronic Arthropathy and Tophaceous Gout

Etiopathogenesis of Gout
Regulation of uric acid

Normal Human Uric Acid Turnover

- Dietary intake
- Normal cellular degradation
- De novo purine synthesis
- Psoriasis
- Malignancy
- Tumor lysis syndrome
- Muscular exercise
- Purine catabolism in other organs (lungs, brain, etc.)

Excretion GI tract (25-33%)

Excretion Kidney (66-75%)
## Causes of hyperuricemia

<table>
<thead>
<tr>
<th>Under-excreters of urate (~90%)</th>
<th>Overproducers of urate (~10%)</th>
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<tbody>
<tr>
<td><strong>Clinical Disorders</strong></td>
<td><strong>Inherited Enzyme Defects</strong></td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>HPRT deficiency</td>
</tr>
<tr>
<td>Lead nephropathy</td>
<td>Increased PRPP synthetase</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>Glucose-6-phosphatase deficiency (glycogenosis I)</td>
</tr>
<tr>
<td>Familial juvenile hyperuricemic nephropathy</td>
<td></td>
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<tr>
<td>Medullary cystic kidney disease</td>
<td></td>
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<tr>
<td>HTN</td>
<td></td>
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<tr>
<td>Dehydration</td>
<td></td>
</tr>
<tr>
<td>Salt restriction</td>
<td></td>
</tr>
<tr>
<td>Starvation</td>
<td></td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>Myeloproliferative disorders</td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td>Lymphoproliferative disorders</td>
</tr>
<tr>
<td>Obesity</td>
<td>Polycythemia vera</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Malignant diseases</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Hemolytic disorders</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Obesity</td>
</tr>
<tr>
<td>Toxemia of pregnancy</td>
<td>Tissue hypoxia</td>
</tr>
<tr>
<td>Bartter's syndrome</td>
<td>Glycogenosis III, V, VII</td>
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<tr>
<td>Chronic beryllium disease</td>
<td></td>
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<tr>
<td>Down syndrome</td>
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</table>

| **Drugs or Dietary Habits**    | **Drugs or Dietary Habits**   |
| Diuretics                      | Ethanol                       |
| Low doses of salicylates       | Diet rich in purines          |
| Ethambutol                     | Pancreatic extract            |
| Pyrazinamide                   | Fructose                      |
| Laxative abuse (alkalosis)     | Nicotinic acid                |
|                                | Ethylamino-1,3,4-thiadiazole  |
|                                | 4-Amino-5-imidazole carboxamide riboside |
|                                | Vitamin B12 (patients with pernicious anemia) |
|                                | Cytotoxic drugs               |
|                                | Warfarin                      |
| Levodopa                       |                              |
| Methoxyflurane                 |                              |
| Cyclosporine                   |                              |
| Tacrolimus                     |                              |
| Ethanol                        |                              |
| Diet rich in purines           |                              |
| Pancreatic extract             |                              |
| Fructose                       |                              |
| Nicotinic acid                 |                              |
| Ethylamino-1,3,4-thiadiazole   |                              |

Urate deposition in the body

Joints
Urate deposition in the body

Tendons
Urate deposition in the body

Bursae
Urate deposition in the body

Ears
Urate deposition in the body

Kidneys

Urate deposition and fibrosis
Urate deposition in the body

Mitral valve
Urate deposition in the body

Small intestine
Mimicking a tumor
Urate burden extends beyond visible tophi

- In addition to visible tophi, MSU crystals can accumulate anywhere in the body
- In a study of 20 patients with gout, significant differences in urate deposits were detected with dual-energy computed tomography (DECT) versus physical examination
  - Only 25% of tophi were detected on physical exam versus DECT
Duel Energy CT (DECT) imaging of urate deposition

DECT imaging show that a majority of gout patients have non-visible tophi.

In a DECT study of 40 patients with non-tophaceous gout, 95% had urate deposits present.

All gout is technically tophaceous

- Systemically, urate crystal deposition initiates the formation of a tophus
- Gout patients are tophaceous by the time the first attack occurs
- Tophi start as small monosodium urate (MSU) aggregates that can only be visualized microscopically

Tophi formation can occur throughout the body, including in organs

Crystal-induced systemic inflammation

1. Macrophage takes in MSU crystals by phagocytosis
2. Activation of NALP3 Inflammasome triggers IL-1β
3. Release of IL-1β triggers neutrophil recruitment and extravasation into the joint space
4. Neutrophil activation leads to the release of proinflammatory compounds
Tophi induces chronic inflammation that can cause bone erosion

- Urate crystal build-up can lead to inflammation and potential destruction of surrounding tissue
- Deposition of urate crystals can lead to destructive skeletal changes

Consequences of untreated or refractory disease

- Invasive surgical intervention
  - Risks and drawbacks
    - High complication rates
    - Delayed wound healing
    - Sepsis/necrosis
    - Potential for worsening
  - Last resort

Treated for osteoarthritis

Photo courtesy of Dr. Brian Mandell, Cleveland Clinic

Treated for rheumatoid arthritis

Photo courtesy of Dr. N Lawrence Edwards, Univ. of Florida
Gout management approach

**RESOLVE Acute Flare**

Treat the acute flare rapidly with an anti-inflammatory agent⁴

**INITIATE Urate-lowering Therapy**

Initiate urate-lowering therapy to achieve serum urate level <6 mg/dL²,³,⁵

Initiate concomitant anti-inflammatory prophylaxis to prevent mobilization flares¹,⁴

**MAINTAIN Treatment to Control sUA**

Continue urate-lowering therapy to reduce the risk of future flares and crystal deposits⁴

Use for up to 6 months while serum urate levels normalize¹
Maintaining SUA <6 mg/dL is associated with reduced risk of recurrent gout flares.
“The best medicine I know for rheumatism is the thank the lord it ain’t gout”

Josh Billings
Appropriate Management of Gout Requires Control of Both Symptoms and Urate Burden

- In order to achieve optimal patient outcomes, it is important to address 2 processes simultaneously
  - Controlling flares and symptoms
  - Reducing the excess body burden of urate

Adequate treatment of excess urate burden may lead to improvement in clinical manifestations\(^32\)
Classes of urate-lowering therapies

Small molecules
- xanthine oxidase inhibitors
  1. allopurinol
  2. febuxostat
- uricosurics
  1. probenecid
  2. lesinurad

Biologic
- pegloticase
Purine catabolism

Almost All Other Mammals

Purines

Hypoxanthine → Xanthine → Urate

Humans

xanthine oxidase

allopurinol
febuxostat

xanthine oxidase

allopurinol
febuxostat

probenecid
lesinurad

Urinary Excretion

Urate

Allantoin

H₂O + O₂ → H₂O₂

plegoticase – uricase replacement

uricase*
2012 ACR Gout Treatment Guidelines

**Treat to Target**
- At minimum, sUA <6 mg/dL
- sUA <5 mg/dL for those with tophi and/or CTGA*

**Durability** improvement in signs and symptoms of gout
- Reduced frequency of flares
- Clearance of tophi

**Pharmacologic ULT Escalation Approach**
- **XOI***
  (Alternative if XOI contraindicated or not tolerated: probenecid)
- sUA target not achieved, continuing disease activity
- Add uricosuric to XOI*
- sUA target not achieved, continuing disease activity
- pegloticase

* Titrated to maximum appropriate dose
Management of refractory gout
The combination of severe gout, high burden of comorbidities, and polypharmacy can make refractory gout challenging to manage.
Patients With Refractory Gout Fail to Achieve Target SUA Levels With Oral ULTs

  - 79% of patients (n=251) on 300 mg allopurinol/day did not meet target sUA <6.0 mg/dL
  - 47% of patients (n=255) on 80 mg febuxostat/day for 52 weeks did not meet target sUA<6.0 mg/dL

- In about 200,000 gout patients, conventional oral urate-lowering agents fail to achieve target uric acid levels

Treatment options for Refractory Gout

- Dose escalation of conventional urate lowering therapies:
  - allopurinol to 800 mg daily in divided doses
  - febuxostat to 160 – 240 mg daily
  - probenecid to 1000 mg daily in divided doses
  - lesinurad to 200 mg daily

- Combination therapy: xanthine oxidase inhibitor + uricosuric

- Lifestyle modifications
  - diet
  - exercise
  - cherry extract
  - vitamin C
  - losartan for diuretics
  - fenofibrate for niacin
  - avoidance of high fructose corn syrup
  - low fat dairy products

- Biologic therapy
  - pegloticase
Pegloticase: a biologic approved for the treatment of refractory gout

- pegloticase is a uric acid-specific enzyme, which is a PEGylated product that consists of recombinant modified mammalian urate oxidase (uricase)
- pegloticase achieves its therapeutic effect by catalyzing the breakdown of uric acid to allantoin
  - allantoin is more water soluble than uric acid and is readily excreted by the kidneys, leading to lowering of sUA levels
- the long-term safety & efficacy profile of pegloticase has been studied in patients receiving treatment for up to 3 years

Figure courtesy of Toby Sannan and Christopher Hadad, Ohio State University.
Purine catabolism

- Hypoxanthine → Xanthine
- Xanthine → Urate
- Urate → Allantoin

Humans:
- Xanthine oxidase
- Allopurinol, Febuxostat
- Probenecid, Lesinurad

Almost All Other Mammals:
- Pegloticase – Uricase replacement
- Uricase

Urine Excretion:
- Hypoxanthine, Xanthine, Urate
Phase III trials - pegloticase

- Two replicate, multicenter, randomized, double-blind, placebo-controlled trials of 6 months duration
  - Subjects included adults with chronic gout refractory to conventional therapy
  - 8 mg pegloticase infusions were studied in two dose regimens (q2wks and q4wks) versus placebo

<table>
<thead>
<tr>
<th>PRIMARY ENDPOINT</th>
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<tbody>
<tr>
<td>• Percentage of plasma uric acid (PUA) responders versus placebo</td>
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<tr>
<td>• Complete Responders</td>
</tr>
<tr>
<td>- Patients who achieved PUA concentration &lt;6 mg/dL for at least 80% of the time during both months 3 and 6</td>
</tr>
<tr>
<td>• Incomplete Responders</td>
</tr>
<tr>
<td>- Patients who did not sustain uric acid levels &lt;6 mg/dL throughout the trial</td>
</tr>
<tr>
<td>- Patients who withdrew before the final visit</td>
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</table>

<table>
<thead>
<tr>
<th>SECONDARY ENDPOINT</th>
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<tbody>
<tr>
<td>• Complete resolution (CR) of tophi</td>
</tr>
<tr>
<td>- Defined as 100% resolution of at least 1 target tophus, with no new or progressive tophi</td>
</tr>
</tbody>
</table>
Phase III trials – Baseline characteristics

• Patient characteristics
  – Mean age: 55 (23-89)
  – Predominantly male (82%)
  – Mean BMI: 33 kg/m

• Patient disease characteristics
  – Mean disease duration: 15 years
  – Mean baseline sUA: 10 mg/dL
  – Mean flares: 10 in prior 18 months (7 in past year)
    • 63% described flares as severe/crippling
  – 71% with visible tophi
Pooled Pivotal Trials Results: Complete Responders

- These patients maintained sUA levels below 6 mg/dL 80% of the time at months 3 and 6 versus 0% for placebo ($P<0.001$)
Pooled Pivotal Trials Results: Incomplete Responders

• These patients achieved a significant reduction in sUA for a mean of 7 weeks, allowing some clearance of the urate burden ($P<0.001$). The response was not durable; therefore, they did not meet the primary endpoint.
Secondary endpoint – Tophus resolution

- 71% of patients had 1 or more tophi at the baseline of the study
Secondary endpoint – Tophus resolution

**SECONDARY ENDPOINT**

**Complete resolution of tophi**
Defined as 100% resolution of at least 1 target tophus, with no new or progressive tophi

At 3 Months

- **22%** of patients (n=62) achieved complete resolution of tophi ($P=0.01$)

At 6 Months

- **45%** of patients treated with pegloticase (q2wk) achieved a complete resolution of their target tophus versus 8% (2/25) of patients receiving placebo ($P=0.002$)

These results include patients who experienced a complete response as well as patients who experienced an incomplete response in the primary endpoint

- **45% (18/40)** of patients treated with pegloticase (q2wk) achieved a complete resolution of their target tophus versus 8% (2/25) of patients receiving placebo ($P=0.002$)
Secondary endpoint – Tophus resolution
Secondary endpoint – Tophus resolution

Baseline

Week 13
Secondary endpoint – Tophus resolution
Secondary endpoint – Tophus resolution
DECT imaging: Resolution of tophi after pegloticase

DECT Imaging of Tophi (Green) in a Responder

Before Treatment

After Treatment

DECT Imaging of Tophi (Green) in a Partial Responder

Before Treatment

After Treatment
### Most Common Serious Adverse Reactions Occurring in at Least 5% of Patients Treated With Pegloticase

<table>
<thead>
<tr>
<th>Adverse Reaction (Preferred Term)</th>
<th>Pegloticase 8 mg q2wk (N=85) n (%)</th>
<th>Placebo (N=43) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gout flare</td>
<td>65 (77)</td>
<td>35 (81)</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>22 (26)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Severe infusion reaction*</td>
<td>4 (5)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

- Other most common adverse reactions occurring in at least 5% of patients treated with pegloticase: nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, and vomiting
Safety: Adverse events

- Most infusion reactions (IRs) occur when sUA levels are >6 mg/dL
- If sUA levels increase to >6 mg/dL on therapy, patient is likely to have anti-pegloticase antibodies, hence an increased risk of infusion reactions
- If sUA is monitored closely and subjects do not receive pegloticase after the sUA has returned to >6 mg/dL, most IRs could be avoided

|                           | Pegloticase 8 mg q2wks  
<table>
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<tbody>
<tr>
<td></td>
<td>N = 22</td>
</tr>
<tr>
<td>sUA &gt;6 mg/dL before infusion reaction</td>
<td>20/22 (91%)</td>
</tr>
<tr>
<td>sUA &lt;6 mg/dL</td>
<td>1/22 (4.5%)</td>
</tr>
<tr>
<td>Infusion reaction at first dose*</td>
<td>1/22 (4.5%)</td>
</tr>
</tbody>
</table>
Safety: Infusion reactions (IRs) and anaphylaxis

- During the pivotal clinical trials, IRs were segmented by severity—mild, moderate, or severe
- IRs occurred in 26% (22/85) subjects treated with pegloticase 8 mg every 2 weeks compared to 5% (2/43) of subjects treated with placebo
- There were 4 cases (5%) of severe IRs identified by physicians that were retrospectively reclassified as anaphylaxis by the FDA*
- Of the 4 cases reclassified as anaphylaxis, 3 likely would have been prevented using the pegloticase sUA stopping rules

* Diagnostic criteria (post-hoc FDA analysis using NIAID/FAAN criteria):
  - Skin or mucosal tissue involvement, and either airway compromise and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to pegloticase or placebo injection with no other identifiable cause
Safety:

- No patients with IRs required intubation, mechanical ventilator support, vasopressors, or hospitalization.

- There were no infusion-related deaths.
Safety: Post-hoc analysis

Most Infusion Reactions Occurred When sUA >6 mg/dL
Pre-infusion sUA Levels Are a Powerful Marker for Predicting IRs

Incidence of IRs per 100 Infusions

<table>
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<tr>
<th>Pegloticase sUA level preceding IR event</th>
<th>IRs per 100 Infusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>2.0</td>
</tr>
<tr>
<td>sUA ≤6 mg/dL</td>
<td>0.5</td>
</tr>
<tr>
<td>sUA &gt;6 mg/dL</td>
<td>4.8</td>
</tr>
</tbody>
</table>

95% of IRs occurred when sUA was >6 mg/dL
Using SUA as a predictive biomarker

Stopping rule:
• Check a SUA 48 hours before the next pegloticase infusion:
  • If SUA <6 mg/dL, infusion can be given
  • If SUA >6 mg/dL, consider discontinuing treatment, particularly when 2 consecutive sUA levels >6 mg/dL are observed

If this stopping rule is utilized, the majority of infusion reactions can be avoided

No other biologic in Rheumatology has a predictive biomarker
Safety: Pre-infusion protocol

**Infusion Premedication**
- Antihistamine the night before and morning of each infusion
- Acetaminophen morning of each infusion
- Corticosteroid prior to each infusion

**Gout Flare Prophylaxis**
- Colchicine, NSAID, or both
- Initiated 1 week before first infusion
- Recommended for at least the first 6 months of therapy

**Oral ULT**
- Discontinue before starting pegloticase

It is important to measure sUA levels prior to infusion
Collaboration between podiatrists & rheumatologists

- Latest treatment options mark a watershed moment in the management of gout
- Podiatrists' role in gout management today is now more critical than ever
  - Increased emphasis on comprehensive, collaborative, and correlated care amongst healthcare providers
  - “First responders” of gout flares
  - Surgical management of refractory tophaceous gout
  - Missing link between a patient’s PCP and rheumatologist
Collaboration between podiatrists & rheumatologists

Results
• 56 podiatrists responded to web-based survey
• Results demonstrated poor integration of podiatrists into multidisciplinary teams
• Only 16% reported being part of an established multidisciplinary team
• 95% expressed interest in professional development for the podiatric management of arthritic conditions

Conclusions
• There are barriers in the involvement of podiatrists in the management of people with rheumatic conditions
Overcoming barriers between podiatrists and rheumatologists in the care of gout patients

• Identify a local rheumatologist who has a common interest in gout

• Foster collaborative relationship
  • Direct contact for referrals and timely consultations
  • Dual podiatry-rheumatology clinics
  • Develop co-management strategy
    • Delineation of roles
    • Identification of common ground
  • Joint community outreach
Summary

• Gout is a chronic, progressive arthritis caused by hyperuricemia with associated chronic inflammation

• Body urate burden extends beyond clinically and physically apparent tophi

• Gout can be difficult to treat, beyond management with xanthine oxidase inhibitors and uricosurics

• Pegloticase is the first biologic and only FDA-approved treatment option for patients with chronic refractory gout

• Pegloticase can be an effective option for patients with chronic refractory gout
Thank you