Hyperuricemia and Gout
An Update on Management

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Goal(s) of treating gout include?

- 1. Maintaining Serum Urate level < 6.0 mg/dl
- 2. Limiting acute flares of gout
- 3. Lowering total body stores or uric acid
- Preventing destructive arthritis due to uric acid deposition in joints
- 4. All of the above

The maximum dose of Allopurinol is?

- 1. 300 mg/day
- 2. 800 mg/day
- 3. Whatever it takes to get urate < 6 mg/dl
- 4. Variable depending on renal function and side effects
- 5. Combination of above options
Medications that inhibit uric acid production include:

1. Allopurinol (Zyloprim)
2. Febuxistat (Uloric)
3. Probenecid
4. Colchicine
5. 1 & 2

Should we be treating asymptomatic hyperuricemia?

1. Yes
2. No
3. Uncertain

Physiologic Urate level

Urate saturation level= 6.8 mg/dl at 37 deg C

Physiologic < 6.8mg/dl at temp < 37 deg C

Urate > Uric acid at levels > 6.8mg/dl

Lab normal up to 8.5

Artistic rendering
**Arthritic Complication of hyperuricemia → gout**

Dr. Theodore Fields, Director Rheumatology Hospital for Special Surgery, New York, NY

**Clinical Manifestations of gout**

**Acute Manifestations**

**Chronic Manifestations**

**Podagra w/ Tophus**

Dr. Theodore Fields, Director Rheumatology Hospital for Special Surgery, New York, NY
Clinical Manifestations of gout
Tophi of the hands

Gout: Radiographic changes
Urate level and gout flares


Diagnosing gout

- Crystal proven
- Not crystal proven
  - Clinical presentation
  - Uric acid > 6.8 mg/dl \textit{not during an acute attack}
  - Tophi present
  - Above w/ classic radiographic changes
  - Risk Factors
    - Family History
    - Diet, Beer intake

Diet and Gout

- Low Purine Diet
  - Beer
  - Red Meat
  - Organ meat
  - Shell Fish
  - Other

- Enhancing urate excretion
  - Vitamin C?
  - Cherry juice?
Vitamin C and Gout

<table>
<thead>
<tr>
<th>Vitamin C intake</th>
<th>Relative Risk</th>
<th>95% Conf Intervals</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>500–999 mg/dl</td>
<td>0.83</td>
<td>0.74–0.92</td>
<td></td>
</tr>
<tr>
<td>1,000–1,499 mg/dl</td>
<td>0.66</td>
<td>0.53–0.86</td>
<td></td>
</tr>
<tr>
<td>&gt; 1,500 mg/dl</td>
<td>0.55</td>
<td>0.38–0.80</td>
<td>P &lt; 0.001 for trend</td>
</tr>
</tbody>
</table>


N=46,994 males followed for 20 years, 1317 incident gout cases, questionnaires

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Treating gout

**Acute Flares**
- Anti-inflammatory medication:
  - **Nsaids**
  - **Colchicine**: not used much today started soon after attack started
  - **Steroids**
    - Oral
    - Injection
- Sufficient doses and duration to control full flare (10-14 days+)
- Analgesics

**Preventing Acute Flares**
- Anti-inflammatory medication:
  - **Nsaids**: low dose daily
  - **Colchicine**: 0.6 mg bid, qd or qod depending on renal function
  - **Steroids**
    - Low dose daily oral
- Start these at time of urate lowering medication
- Continue for minimum 6 mo

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Treating Acute Flares

- **Nsaids** – any one will do
  - High enough dose
  - Long enough treatment
  - Limited in renal insufficiency, anti-coagulation, CHF etc
- **Colchicine**
  - NO LONGER 1 every hour until diarrhea
  - Rather ~ 1 bid to tid for several days then back to 1 bid
  - Better for long term inhibition against flares
- **Steroids**
  - Steroid taper or injection if just one joint
Long term control of disease

- Probenecid – enhances urate renal clearance
  - Bid to tid
  - Some drug interactions
  - Works best if urine alkaline
  - Not for hyperexcreters (~10%)
- Allopurinol – purine analog- xanthine oxidase inhibitor
  - Dose 1-2 every day
  - Minimal drug interactions
  - No trouble w/ acid or alkaline urine
- Uloric- non purine analagog- xanthine oxidase inhibitor

When to initiate Urate Lowering therapy

- Some suggest after 1st attack
- Multiple attacks
- Tophi
- Destructive changes on radiographs
- Concomitant diseases

- Start once acute attack subsides

Urate lowering therapy: Follow up testing

- Recheck Urate level minimum 2 weeks – typically 1 mo
- Adjust medication dose to achieve urate level < 6 mg/dl
- Monitor urate level once or twice a year to assure compliance
- Monitor renal, LFTs, CBC once or twice yearly

- No need to stop therapy for flares
Losartan and uricosuric effects

Losartan molecule (no metabolite) interferes w/ urate resorption in proximal tubule $\rightarrow$ enhanced urate excretion and lowers Serum UA $^{(6,7,3)}$

LIFE study (Losartan Intervention for Endpoint reduction in HTN) demonstrated that Serum uric acid was associated w/ CV events and that losartan had lower UA than atenolol and may have accounted for better CV results. $^4$

Other ARBs have not shown same effect on lowering SUA or increasing excretion UA $^5$

2. Soffer BA Hypertension 1995;26
3. Weber MA Arch Int Med 1995;155
4. Hoeggan A Kidney Int 2004;65
5. Puig JG Hypertens 1999;17

Fenofibrate and lowering uric acid

Fenofibrate has been shown to increase uric acid excretion and lower serum uric acid and decrease episodes gout $^{1,2}$

Effect not seen w/ benzaflbrate – thought therefore not to be the lipid lowering effect $^3$

Fenofibrate has been shown to enhance urate reduction in males treated w/ allopurinal $^4$

3. Bastow MD. Metabolism 1988;37
4. Feher MD. Rheumatology 2003;42.
5. Takahashi S. Ann Rheum Dis 2003;62

Allopurinol: Xanthine Oxidase inhibitor

- Protein Binding < 1%
- 75% metabolized by liver to active metabolite Oxypurinol
- Excretion: Urine 76% as Oxypurinol; 12% as unchanged drug
Allopurinol Renal Dose adjustments

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Maintenance Dose of Allopurinol (mg) / day</th>
</tr>
</thead>
<tbody>
<tr>
<td>140</td>
<td>400</td>
</tr>
<tr>
<td>120</td>
<td>350</td>
</tr>
<tr>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td>80</td>
<td>250</td>
</tr>
<tr>
<td>60</td>
<td>200</td>
</tr>
<tr>
<td>40</td>
<td>150</td>
</tr>
<tr>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>0</td>
<td>100 every 3 days</td>
</tr>
<tr>
<td>0</td>
<td>100 every 1 days</td>
</tr>
</tbody>
</table>

*This table is based on a standard maintenance dose of 300 mg of allopurinol per day for a patient with a creatinine clearance of 100 mL/min. (Package Insert)

Advantages of Allopurinol

- Effective for both overproducers and underexcretors
- Convenience of single daily dose
- Can be efficacious in patients with renal insufficiency

Limitations of Allopurinol

- "Standard" doses may not achieve target serum urate
  - In one study, only 73% of allopurinol (300 mg qd) patients achieved target serum urate <6 mg/dL
  - Higher doses were effective
- Need for dose adjustment according to renal function
  - Metabolites are excreted by the kidney. Accumulation can occur with renal insufficiency
- Precipitation of an acute attack
  - Lowering serum urate mobilizes deposited crystals

Limitations of Allopurinol

- Adverse effects
  - Rash
  - GI intolerance (diarrhea, nausea)
  - Increase in transaminases
  - Bone marrow suppression (uncommon)
  - Severe hypersensitivity syndrome
    - Occurs early in treatment
    - Infrequent, but life threatening (20% mortality)
    - Multi-symptom involvement - fever, rash, decreased renal function, vasculitis, hepatocellular injury, leukocytosis, and eosinophilia
    - Immediate drug withdrawal and supportive therapy

Febuxistat (Uloric)

- ULORIC has a nonpurine structure and is the first branded drug in 40 years for the treatment of hyperuricemia in gout patients
- ULORIC is not expected to inhibit other enzymes involved in purine/pyrimidine synthesis and metabolism at therapeutic doses

Febuxistat (Uloric)

- Xanthine Oxidase Inhibitor
- Metabolized by liver
  - Glucuronidation
  - Cytochrome P450 (not 2D6)
- No drug interactions w/ Warfarin, Colchicine, Naproxen, Indomethacin, desipramine, HCTZ
- Excreted 45% feces; 49% inactive drug via kidney
- Only 3% unmetabolized drug excreted via kidney
- NO dose adjustment needed for renal insufficiency (creatinine clearance ~ 30cc/min)
Demographics for 3 phase 3 febuxistat trials

<table>
<thead>
<tr>
<th>Feature</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>95%</td>
</tr>
<tr>
<td>Race: Caucasian</td>
<td>80%</td>
</tr>
<tr>
<td>African American</td>
<td>10%</td>
</tr>
<tr>
<td>Ethnicity: Hispanic or Latino</td>
<td>7%</td>
</tr>
<tr>
<td>Alcohol user</td>
<td>67%</td>
</tr>
<tr>
<td>Mid-to-moderate renal insufficiency</td>
<td>59%</td>
</tr>
<tr>
<td>(percent with estimated Clcr &lt; 50 ml/min)</td>
<td></td>
</tr>
<tr>
<td>History of hypertension</td>
<td>49%</td>
</tr>
<tr>
<td>History of hyperlipidemia</td>
<td>38%</td>
</tr>
<tr>
<td>BMI ≥30 kg/m²</td>
<td>63%</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>33 kg/m²</td>
</tr>
<tr>
<td>Mean age</td>
<td>52</td>
</tr>
<tr>
<td>Mean baseline sUA</td>
<td>8.7 mg/dL</td>
</tr>
<tr>
<td>Experienced a gout flare in previous year</td>
<td>85%</td>
</tr>
</tbody>
</table>

*In the phase 3 trials APEX, FACT, and CONFIRM.

Febuxistat vs Allopurinol

Proportion of Subjects With sUA <6 mg/dL at Final Visit

![Febuxistat vs Allopurinol Chart]

Tekada Package insert

Febuxistat vs Allopurinol

Proportion of Subjects With sUA <6 mg/dL at Final Visit

![Febuxistat vs Allopurinol Chart]

Tekada Package insert
Febuxistat vs Allopurinol: Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Placebo (n=134)</th>
<th>ULORIC 40 mg daily (n=757)</th>
<th>ULORIC 80 mg daily (n=1279)</th>
<th>Allopurinol 300/200 mg daily (n=1277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver Function Abnormalities</td>
<td>0.7%</td>
<td>6.6%</td>
<td>4.6%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.7%</td>
<td>1.1%</td>
<td>1.3%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>0%</td>
<td>1.1%</td>
<td>0.7%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Rash</td>
<td>0.7%</td>
<td>0.5%</td>
<td>1.6%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

*All 24.5% greater rate than with placebo.

Febuxistat vs Allopurinol: Adverse Reactions

- During phase 3 studies, transaminase elevations greater than 3 times the upper limit of normal (ULN) were observed.
- No dose-effect relationship for these elevations was noted.

<table>
<thead>
<tr>
<th>ALT and/or AST ≥3 × ULN</th>
<th>ULORIC</th>
<th>Allopurinol</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>ALT</td>
<td>3%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Tekada Package insert
Febuxistat vs Allopurinol: Adverse Reactions

Cardiovascular Events: In randomized controlled studies, there was a higher rate of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) in patients treated with ULORIC [0.74 per 100 P-Y (95% CI 0.36-1.37)] than allopurinol [0.60 per 100 P-Y (95% CI 0.16-1.53)]. A causal relationship with ULORIC has not been established. Monitor for signs and symptoms of MI and stroke.

The Future of the Treatment of Hyperuricemia: Uricase Enzymes

- Uricase enzymes further catabolize uric acid to a more soluble, readily excretable form
- Agents available
  - Include rasburicase and aspergillus uricase (ex-US)
  - PEGylated recombinant uricases in phase II clinical trials
    - Polyethylene glycol (PEG) modification reduces antigenicity and prolongs half-life

The Future of the Treatment of Hyperuricemia: Uricase Enzymes

- Rasburicase
  - Not indicated for hyperuricemia of gout
  - Indicated for management of hyperuricemia in tumor lysis syndrome of pediatric oncology
  - Studies show dramatic reductions in uric acid levels
  - Potential for immunogenicity and subsequent fatalities

Black box warnings for anaphylaxis, hemolysis, and methemoglobinemia


Controversies related to gout/hyperuricemia

- Should asymptomatic hyperuricemia be treated?
- Is there a physiologic relationship between hyperuricemia and HTN?
- Is hyperuricemia an innocent bystander of an independent predictor of ASCAD and mortality?

Co-morbidities Associated With Hyperuricemia

- Obesity
- Metabolic syndrome
- Diabetes mellitus
- Heart failure
- Hyperlipidemia
- Hypertension

Hyperuricemia & Hypertension
A Potential Explanation of Association (cont’d)

- Effects on the afferent arteriole after 5 weeks
  - Uncontrolled hyperuricemia: Arteriole thicker, lumen smaller
  - Controlled hyperuricemia: Arteriole thinner, lumen larger

- Association to glomerular hypertension may be caused by afferent arteriole thickening
  - Suggestive of hypertrophic vascular remodeling

Studies w/ significant association between high uric acid preceding HTN and found to be independent predictor

- Bogalusa Hrt Study n=550 children 12yr f/u Alper AB Hypertens 2005;45:34-38
- Kaiser Permanete Medical Care Program n=1031 RR 2.19 Salty J Am J Epidemiol 1993;131:1027-27
- Utah HTN Screening n=3482 RR 2.06 Hunt CS Hypertens 1994;27:969-76
- Olivetti Heart Study n=619 Italian men RR 1.23 Jossa F J Hum Hypertens 1994;8:67-81
- Osaka Health Survey n=6356 Japanese males RR 2.01 Taniguchi Y J Hypertens 2000;19:1209-15

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