Losartan as an Adjunct for Lowering Uric Acid Levels in Hypertension and Gout

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Disclosure Statement

• Paulina Nguyen, PharmD, MBA

• No conflict of interest

• Presentation is educational in nature and abides by non-commercial guidelines

Learning Objectives

• Review pathophysiology of uric acid production and excretion

• Understand the association between hypertension and gout

• Describe the mechanism of using losartan as adjunctive management of hyperuricemia & gout

• Target Audience: Pharmacists
Pre-Test Question

1. Approximately how many patients with hypertension will develop gout?
   a) 10
   b) 5.4
   c) 2.31
   d) 6.24
   e) None of the above

2. True or False: All angiotensin-receptor blockers lower serum uric acid levels.

Background

• Humans cannot convert uric acid into soluble form, thus increasing risk for:
  - Hyperuricemia
  - Uric acid crystallization in joints and tissues

• There are two mechanisms for hyperuricemia

Background - Hyperuricemia

• Hyperuricemia has an unclear definition based on serum uric acid level

• Target thresholds for serum urate: Urate is soluble up to ~6.8 mg/dL.

• If urate levels >6.8 mg/dL, precipitation may occur.
  - Threshold is not an absolute indicator of asymptomatic hyperuricemia or gout flare*
Concerns over Hyperuricemia and Gout

- Over time, high serum urate levels may lead to gout
- Majority of people with hyperuricemia never develop symptoms associated with uric acid excess
- Data from Normative Aging Study in 1987:
  - ~1858 previously healthy men (average age ~ 42 years)
  - ~<5% incidence of gout for majority of patients


Gout Treatment and Prophylaxis

- Treatment and prophylaxis includes medications such as:
  - Xanthine Oxidase Inhibitors (e.g. allopurinol, febuxostat)
  - Uricase agents (e.g. pegloticase)
  - Uricosuric agents (e.g. probenecid)
  - Other: Colchicine

- Targeting serum uric acid (SUA) <6 mg/dL in urate lowering therapy outside of acute gout flare to:
  - Prevent development of tophi
  - Reduce risk of flare

Gout Treatments – Urate Lowering Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>MOA</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>Xanthine Oxidase inhibitor - serum levels and urinary levels of uric acid</td>
<td>Starting dose: 100 mg/day (30-50 mg/day in stage 4 CKD)</td>
</tr>
<tr>
<td>Febuxostat</td>
<td>Starting dose: 40 mg daily</td>
<td>Maintenance: 40-80 mg daily (depending if uric acid levels &lt; 6 mg/dL achieved after 2 weeks with 40 mg dose)</td>
</tr>
<tr>
<td>Probenecid</td>
<td>URAT1 and GLUT9 inhibitor – inhibition of tubular reabsorption of filtered urate in kidney to control hyperuricemia &amp; prevent tophus formation</td>
<td>Initial: 250 mg BID x 1 wk</td>
</tr>
<tr>
<td>Pegloticase</td>
<td>Recombinant, PEGylated uricase – converts uric acid to allantoin for renal excretion</td>
<td>8 mg IV every 2 weeks</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Anti-inflammatory agent that targets neutrophils</td>
<td>1.2 mg at first sign of flare then 0.6 mg 1 hour later</td>
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Gout and Hypertension

- Hypertension is a common comorbidity seen in hyperuricemia & gout
  - Patients with hypertension are 2.31 times more likely to develop gout
  - Approximately 74% of gout patients have hypertension

- Hypertension is an independent risk factor for developing gout

- Anti-hypertensives such as ACE Inhibitors, diuretics, etc. are typically associated with hyperuricemia

Gout and Hypertension: Proposed Mechanisms

1. SUA has been proposed as one of the precursors of hypertension as a result of renal dysfunction causing both increased blood pressure and increased SUA.

2. A 2002 patient case-control study set in northern California found that hypertension incidence was significantly associated with increased SUA levels
   - As such, SUA was hypothesized to be either a marker or intermediate step in the hypertension pathophysiological pathway

3. Hypertension-associated elevated serum lactate levels may increase SUA
   - Initial renal microvascular disease
   - Local tissue hypoxia
   - Increased lactate
   - Decreased uric acid tubular secretion
   - Increased SUA levels

4. Increased uric acid secretion may be caused by intrarenal ischemia via xanthine oxidase.

5. Metabolic states such as hyperinsulinemia or increased sympathetic activity activate renin-angiotensin system (RAS)
   - Activation of RAS leads to:
     - Increased arterial pressure
     - Decreased renal blood flow
     - Decreased uric acid secretion
     - Increased purine oxidation
     - Decreased uric acid excretion
     - Increased reactive oxygen species
     - Vascular injury
     - Reduced nitric oxide
     - Increased SUA levels
Why Have Adjunctive Gout Therapies?

- Rates of gout in USA increased during the 1990s—especially for men older than 75 years in whom rates nearly doubled from 2.1% in 1990 to 4.1% in 1999.
- In USA 2.6 million in 2005, projected to increase to 3.6 million in 2025.
- Diminished patient quality of life with gout flares

Suboptimal Control of Hyperuricemia or Persistent Gout Flares

Possible reasons include:
- May be intolerant of allopurinol
- On medications that exacerbate hyperuricemia and possibly increasing risk of gout flares

WHAT OPTIONS ARE THERE FOR HYPERTENSIVE PATIENTS WITH GOUT?

Losartan to the rescue...

- Losartan has been shown to decrease serum uric acid levels anywhere from 10-15% to 20-25%.
  - One 2001 study has shown that losartan aids in decreasing serum uric acid levels by about 10-15%.
  - Studies from 1993-2001 showed an approximate 20-25% decrease in serum uric acid levels.
- The uricosuric effect of losartan was not found to be dose-dependent (100 mg/day did not appear to be more effective than 50 mg/day).
- Uric acid-lowering effect was not seen with other angiotensin II receptor blockers.
- Also prevents kidney stone formation from hyperuricemia through alkalization of urine pH.
- 2011 retrospective post-hoc study showed renal protective effect.
Theoretical Mechanism of Losartan In Management of Hyperuricemia

- **Mechanism:**
  - Increase urinary uric acid excretion to lower serum uric acid levels ("uricosuric")
  - Blocks human urate transporter 1 (URAT1) levels
    - URAT1 is transporter of urate across renal tubule lumen
  - Causes decrease in net urate reabsorption in the proximal tubule

2012 American College of Rheumatology Guidelines

- "Use of agents other than probenecid with clinically significant uricosuric effects, such as fenofibrate and losartan, can be therapeutically useful as components of a comprehensive ULT strategy"
- Recommendations for case scenarios of refractory disease in gout include: "Effective therapeutic options include addition of a uricosuric agent (e.g., probenecid, fenofibrate, or losartan) to an xanthine-oxidase inhibitor drug"

Post-Test Assessment Questions

1. Approximately how many patients with hypertension will develop gout?
   a) 10
   b) 5.4
   c) 2.31
   d) 6.24
   e) None of the above

2. True or False: All ARBs lower uric acid levels.
Take-Away Points

- Losartan decreases SUA levels by ~10-25% compared to placebo
- Uricosuric effect of losartan does not appear to be dose-dependent
- Losartan may be a useful urate-lowering adjunctive therapy in gout patients with concomitant hypertension
- Further studies needed on effect of losartan uricosuric effects on clinical outcomes of hypertensive gout patients

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