Does Starting Allopurinol Prolong Acute Treated Gout?

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Disclosure slide

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- No commercial financial relationships to disclose

Introduction

- Traditional teaching discourages initiation of urate-lowering therapy during an acute gout attack
- Reference textbooks for clinical practice and education support this principle
- The 2012 ACR Guidelines for Management of Gout recommended that urate-lowering therapy could be started during an acute gout attack, evidence C

Methods

Subject selection

Inclusion criteria:
1. Crystal proven gout
2. Acute attack within 72 hours of first treatment

Plus one of the following:
1. ≥ 2 gout attacks in past 12 months OR
2. Tophus, nephrolithiasis, or 24hr urine uric acid > 1000mg

Exclusion criteria:
1. Inability to return for examinations
2. GFR < 50mL/min
3. Allopurinol use in past 6 months
4. Ongoing cancer therapy
5. Concomitant azathioprine or cyclophosphamide
6. AST/ALT or alk phos > 1.25 x upper limit of normal
7. Pre-morbid pain in involved joint of > 3 on a scale of 1-10
8. Neurologic deficit around joint

Intervention

- Primary physician initiated acute gout treatment
- Randomized to placebo or allopurinol for 28 days
  - Allopurinol: 1 tab (100mg) daily x 14 days, then 2 tabs (200mg) daily x 14 days
  - Placebo: 1 tab daily x 14 days, then 2 tabs daily x 14 days
- Standard prophylaxis: colchicine 0.6mg once to twice daily or meloxicam 15mg daily
**Methods**

**Measurements**

- Patients assessed over 5 visits in 28 days
- Primary endpoint: Time to resolution of acute gout defined as all of the following:
  1. Involved joint pain < 3 on a 10-point Likert scale or 50% reduction from study initiation
  2. Score of 0 swelling, 0 warmth, and 0 to 1 tenderness on a 3-point physician rated Likert scale (S0 W0 T0-1)
  3. No new inflammation in any other joints

**Methods**

**placebo control**

- Identical capsules
- Blinding Monitoring
  - Blinding success was assessed at last visit by asking investigator and subject to guess the subject's group assignment
    - Statistically insignificant correct/incorrect guess rate
  - The treating physician was blinded to lab results after an interim analysis

**Methods**

**Statistics**

- Intent to treat
  - Maximizing differences between groups
    - Inputting maximum days (28) for allopurinol drop-outs and actual days to resolution for placebo drop-outs
  - Per protocol (completer) analysis also performed
- Pre-Study power analysis: 32 patients needed to detect a 2-day difference with 80% power
- Mann-Whitney U analysis to compare the primary endpoint between groups

**Results**

**Demographic data**

- Baseline characteristics were similar between the two groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo Group (n = 19)</th>
<th>Allopurinol Group (n = 16)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (range)</td>
<td>53.11 (31-68)</td>
<td>60.63 (40-84)</td>
<td>0.06</td>
</tr>
<tr>
<td>Male (%)</td>
<td>19 (100)</td>
<td>14 (87.5)</td>
<td>0.2</td>
</tr>
<tr>
<td>Mean disease duration, years (range)</td>
<td>4.89 (0-17)</td>
<td>5.5 (0-20)</td>
<td>0.74</td>
</tr>
<tr>
<td>Mean number of previous gout attacks (range)</td>
<td>6.58 (1-35)</td>
<td>3.67 (0-12)</td>
<td>0.24</td>
</tr>
<tr>
<td>Nephrolithiasis (%)</td>
<td>1 (5.26)</td>
<td>4 (25)</td>
<td>0.16</td>
</tr>
<tr>
<td>Tophi (%)</td>
<td>6 (31.6)</td>
<td>6 (37.5)</td>
<td>0.74</td>
</tr>
<tr>
<td>Erosions (%)</td>
<td>4 (21.05)</td>
<td>4 (25)</td>
<td>1</td>
</tr>
</tbody>
</table>
Results

Initial treatment

- Primary physician initiated acute treatment
- Treatment similar between groups

<table>
<thead>
<tr>
<th>Initial treatment (%)</th>
<th>Placebo</th>
<th>Allopurinol</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM steroid</td>
<td>8 (42.1)</td>
<td>10 (62.5)</td>
</tr>
<tr>
<td>Intraarticular steroid</td>
<td>8 (42.1)</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>PO steroid</td>
<td>2 (10.5)</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>NSAIDs + colchicine</td>
<td>0 (0)</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>NSAID monotherapy</td>
<td>3 (15.8)</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>

P = 0.23 for two groups by Fisher Exact Test 2x5 table

Results

Primary endpoint

- Intent-to-treat analysis showed 4.5 days longer to resolution in the allopurinol group, however difference not significant
- Difference was reduced to 2 days in the per protocol analysis

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Allopurinol</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>(n=19)</td>
<td>12.53 (7.73)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>3, 24</td>
<td>3, 28</td>
</tr>
</tbody>
</table>

Per Protocol Group | (n=17) | (n=14) | 0.5 |
| Mean (SD) | 13.44 (7.78) | 15.43 (7.92) |
| Min, Max | 3, 24 | 3, 28 |

1 Mann-Whitney U, 2 All patients randomized, 3 Patients who completed protocol

Results

Secondary endpoints

- Both groups had similar patient rated Likert pain scores at enrollment and at day 28

Results

Secondary endpoints

- Baseline mean levels of serum uric acid were 8.16mg/dL in the allopurinol group and 7.95mg/dL in the placebo group

Results

Secondary endpoints

- Both groups had similar physician global assessment (PGA) scores

Results

Secondary endpoints

- Baseline mean levels of serum uric acid were 8.16mg/dL in the allopurinol group and 7.95mg/dL in the placebo group
Adverse events

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Placebo Group (n = 19)</th>
<th>Allopurinol Group (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Elevated aminotransferase</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total (%)</td>
<td>2 (10.5%)</td>
<td>1 (6.25%)</td>
</tr>
</tbody>
</table>

Study Limitations

- Initial treatment was not uniform
  – Intended to mimic real world practice
- Excluded GFR < 50mL/min
  – May not apply when patient cannot take prophylaxis due to reduced GFR

Conclusions

- Initiating allopurinol during an acute treated gout attack did not adversely affect the outcome
- Our results support the ACR 2012 recommendations for the management of gout

References

1. Firestein GS, Budd RC, Gabriel SE, McInnes IB, O’Dell JR. Firestein: Kelley's textbook of rheumatology. 9th ed. Ch 95. 2012