Gout: Update in therapeutics

29/11/2014
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Summary

• Why treating gout?
• Guidelines: ACR 2012
• Drugs:
  • Colchicine
  • Allopurinol: what about the kidney?
  • Febuxostat

A little history...

• 2600 BC Egypte (Eber’s papyrus)
• 400 BC Hippocrates: Podagra
• 500 BC Colchicine (Alexander of Tralles)
• 1200 Randolphus of Bocking, ‘gutta’
• 1679 van Leeuwenhoek urate crystals
• 1763 Baron Anton von Storck of Vienna
• 1950s Allopurinol, Georges Hitchings and Gertrude Elion

Treatment... but why?

• Gout is a chronic disease
• Prevent flares
• And this

Treatment... but why?

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Velocity of Tophi Reduction

Perez-Ruiz, Arthritis Care & Res 2002
Treatment…but why?

• Gout is a chronic disease
• Prevent flares
• And this: tophi
• Better cardiovascular outcome?

2012 ACR Management Guidelines for Acute Gouty Arthritis

The choice of pharmacologic agent depends on severity of the attack
• Monotherapy for mild/moderate attack
• Combination therapy for severe attack or those refractory to monotherapy
• Acceptable combination therapy approaches include
  • Colchicine and NSAIDS
  • Oral steroids and colchicine
  • Intra-articular steroids with all other modalities
• Continue current therapy during flare
• Patient education on signs of flare for self treatment
• Cold packs

Pathophysiology

Hyperuricemia
Overproduction

Underexcretion

20-30%

~2%

Metabolic syndrome
Cardiovascular events

AGREE study: Acute Gout Flare Receiving Colchicine Evaluation

• High vs. Low Dose Colchicine for Gout Flare
• Randomized, double-blind, placebo-controlled study
• Low dose colchicine (1.8mg total over 1 h)
• High dose colchicine (4.8mg total over 6 h)
• Primary endpoint: >50% pain reduction in 24 hours without rescue medication
• 184 patients intent-to-treat analysis


Colchicine

Dose

% >50% reduction in pain

P value vs. placebo

Adverse Event Rate

% needing rescue medications

<table>
<thead>
<tr>
<th>Dose</th>
<th>% &gt;50% reduction in pain</th>
<th>P value vs. placebo</th>
<th>Adverse Event Rate</th>
<th>% needing rescue medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose</td>
<td>32.7%</td>
<td>0.034</td>
<td>71.9%</td>
<td>34.8%</td>
</tr>
<tr>
<td>Low dose</td>
<td>37.8%</td>
<td>0.005</td>
<td>36.5%</td>
<td>31.1%</td>
</tr>
<tr>
<td>Placebo</td>
<td>15.5%</td>
<td>n/a</td>
<td>27.1%</td>
<td>50.0%</td>
</tr>
</tbody>
</table>

Adverse Events | High Dose | Low Dose | Placebo |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All GI Events</td>
<td>76.9</td>
<td>25.7</td>
<td>20.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>76.9</td>
<td>23.0</td>
<td>13.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>17.3</td>
<td>4.1</td>
<td>51.1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17.3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Improvement in pain @ 24 hours

Conclusion

• Low-dose colchicine had similar efficacy to high-dose colchicine with lower adverse effect profile.


Colchicine toxicity

• No dose reduction in mild to moderate renal disease
• Contra-indicated in combination with CYP3A4 inhibitors (grapefruit) or P-glycoprotein
• Drugs: clarythromycin, erythromycin, cyclosporine, verapamil
• Diarrhea: not just a side effect, but due to toxicity!

2012 ACR Management Guidelines

• Lifestyle Modification for all patients with gout, elimination of non-essential drugs that cause hyperuricaemia
• Xanthine Oxidase Inhibitor (XOI) first-line urate-lowering pharmacologic therapy
• Target sUA <6 at minimum, sUA <5 better (tophi)
• Starting dose of allopurinol should be 100mg, less in CKD with titration above 300mg prn if needed (even in CKD)
• Continue prophylaxis for 3–6 months (tophi) after achieving target sUA (0.5–1mg per day)


Drugs that can cause hyperuricemia:
- Diuretics
- Cyclosporine
- Low dose aspirin
- Ethambutol/pyrazinamide
- Levodopa
- Heparin

Azathioprin is contra-indicated with allopurinol

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- Starting dose of allopurinol should be 100mg, less in CKD with titration above 300mg prn if needed (even in CKD)
- Continue prophylaxis for 3 (no tophi) – 6 months (tophi) after achieving target sUA (0.5-1mg per day)

2012 ACR Management Guidelines

- Consider HLA screening for HLA-B*5801 in certain populations considered high risk for allopurinol hypersensitivity syndrome
- Koreans with stage 3 CKD or worse
- Han Chinese
- Thai descent
- Combination oral ULT with 1 XOI agent and 1 uricosuric agent is appropriate when sUA not at target by XOI alone
- Pegloticase appropriate for severe refractory disease or intolerance of standard regimens

Urate-lowering therapy

Allopurinol

What about the toxicity, especially in renal insufficiency?

Allopurinol Hypersensitivity Syndrome

- 2% of all allopurinol users develop cutaneous rash
- Frequency of hypersensitivity 1 in 260
- DRESS syndrome
- Drug reaction, eosinophilia, systemic symptoms
- 20% mortality rate
- Life-threatening toxicity: vasculitis, rash, eosinophilia, hepatitis, progressive renal failure
- Treatment: early recognition, withdrawal of drug, supportive care (steroids, N-acetyl-cysteine, dialysis)
- Risk factors: recent commencement, female sex, age, HLA-B*5801, diuretics, low dose less risks

Allopurinol and Renal Insufficiency

- “Avoidance of allopurinol or use of reduced doses in patients with renal insufficiency according to proposed guidelines should be adequate to inhibit uric acid production in most patients and may reduce the incidence of life-threatening allopurinol toxicity.”
Maintenance Doses of Allopurinol for Adults based on CrCl

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Maintenance Dose of Allopurinol</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>100 mg every 3d</td>
</tr>
<tr>
<td>10</td>
<td>100 mg every 2d</td>
</tr>
<tr>
<td>20</td>
<td>100 mg</td>
</tr>
<tr>
<td>40</td>
<td>150 mg</td>
</tr>
<tr>
<td>80</td>
<td>200 mg</td>
</tr>
<tr>
<td>100</td>
<td>300 mg</td>
</tr>
<tr>
<td>120</td>
<td>350 mg</td>
</tr>
<tr>
<td>140</td>
<td>400 mg</td>
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</tbody>
</table>


What did doctors take home?

- Guidelines made in order to prevent allopurinol hypersensitivity
- Allopurinol should not be used in renal insufficiency

Allopurinol Use in Renal Insufficiency

- Objective:
  - Determine the safety and efficacy of increasing allopurinol dose above the proposed guidelines for patients with gout
  - Prospective study of patients on allopurinol ≥ 1 month
  - 81.9% European, 14.4% Maori or Pacific Island Descent
  - Saw patients monthly and titrated allopurinol until sUA <6 for 3 months then q3 months


Is recommended dose of allopurinol enough?

- 19% (recommended) vs 38% (higher than recommended) reached sUA <6, p <0.01
- 4/250 (1.6%) developed hypersensitivity (All took recommended doses)


Allopurinol Use in Renal Insufficiency

- Mean baseline dosage
  - 221.4 mg (range 100-400, median 200)
- Mean dose for pts who completed study
  - 335.7 mg (range 0-600, median 350)
- Mean dose for pts who achieved sUA <6
  - 359.7 mg (range 150-600, median 450)

Conclusions

• Doses above recommended dose are effective for lowering sUA with few adverse events

• Patients with renal impairment tolerated allopurinol doses higher than CrCl-based doses and achieved sUA <6

• Monitor sUA regularly and treat-to-target sUA <6

• Limitations of study: self-selected patients who were already on allopurinol → minimize incidence of toxicity


AHS: association with starting dose

<table>
<thead>
<tr>
<th>Dose</th>
<th>% of patients with sUA &lt;6.0 mg/dl (&lt;0.36 mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>3%</td>
</tr>
<tr>
<td>Febuxostat 80 mg</td>
<td>7%</td>
</tr>
<tr>
<td>Febuxostat 120 mg</td>
<td>17%</td>
</tr>
<tr>
<td>Allopurinol 300 mg</td>
<td>22%</td>
</tr>
</tbody>
</table>

*Within-controlled allopurinol 300 mg group, allopurinol 100 mg efficacy: 0%; allopurinol 300 mg efficacy: 23%. ITT population recruited with serum urate level >8.0 mg/dl at day 2.

Stamp LK A&R 2012

Febuxostat

Figure 2: Sample size distribution of patients in APEX trial. The study comprised 960 patients with gout and an elevated baseline serum urate level (≥8.0 mg/dl). Patients were randomized to one of three dose groups: placebo, 80 mg/day of Febuxostat, or 120 mg/day of Febuxostat. Serum urate levels were measured at baseline and every 3 months until the end of the study. Patients were considered to have achieved urate target if their urine urate level was <6.0 mg/dl (<0.36 mmol/l) at any point during the study. Schumacher HR, et al. Arthritis Rheum 2008; 58:1344-1354.

Febuxostat

APEX trial (6 months)

proportion of patients with sUA <6.0 mg/dl (<0.36 mmol/l)

<table>
<thead>
<tr>
<th>Dosage</th>
<th>% of patients with sUA &lt;6.0 mg/dl (&lt;0.36 mmol/l)</th>
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</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0%</td>
</tr>
<tr>
<td>Febuxostat 80 mg</td>
<td>10%</td>
</tr>
<tr>
<td>Febuxostat 120 mg</td>
<td>40%</td>
</tr>
<tr>
<td>Allopurinol 300 mg</td>
<td>50%</td>
</tr>
</tbody>
</table>

*Within-controlled allopurinol 300 mg group, allopurinol 100 mg efficacy: 0%; allopurinol 300 mg efficacy: 23%. ITT population recruited with serum urate level >8.0 mg/dl at day 2.

Richette, Nat R 2014
**CONFIRMS : Primary endpoint**

proportion of subjects with sUA lower than 6.0 mg/dl and 5.0 mg/dl at 6 months

- Febuxostat 40 mg
- Febuxostat 80 mg
- Allopurinol 300/200 mg

<table>
<thead>
<tr>
<th>Drug</th>
<th>≤ 6.0 mg/dl</th>
<th>≤ 5.0 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febuxostat 40 mg</td>
<td>45%</td>
<td>17%</td>
</tr>
<tr>
<td>Febuxostat 80 mg</td>
<td>67%</td>
<td>44%</td>
</tr>
<tr>
<td>Allopurinol 300/200 mg</td>
<td>42%</td>
<td>13%</td>
</tr>
</tbody>
</table>

*p<0.001 vs allopurinol
†p<0.001 vs febuxostat 40 mg
§Febuxostat 40 mg is not marketed in Europe.

**CONFIRMS : Secondary endpoint**

proportion of subjects with sUA ≤ 6.0 mg/dl at final visit analysed by renal function: moderate vs mild vs normal

- CrCl 30–59 ml/min (moderate)
- CrCl 60–89 ml/min (mild)
- CrCl >89 ml/min (normal)

<table>
<thead>
<tr>
<th>Function</th>
<th>≤ 6.0 mg/dl</th>
<th>≤ 5.0 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl 30–59 ml/min (moderate)</td>
<td>43%</td>
<td>71%</td>
</tr>
<tr>
<td>CrCl 60–89 ml/min (mild)</td>
<td>32%</td>
<td>52%</td>
</tr>
<tr>
<td>CrCl &gt;89 ml/min (normal)</td>
<td>46%</td>
<td>37%</td>
</tr>
</tbody>
</table>

**Take Home Message**

- Gout is a chronic disease
- Target sUA ≤ 6 at minimum, sUA < 5 better (tophi)
- Allopurinol: start low, go slow
- Allopurinol: even in renal insufficiency
- Febuxostat: don’t forget the colchicine!
- Finally: check cardiovascular risk factors!