69yo man with CAD, HTN, CKD, MGUS, EtOH abuse [1/5 of liquor per week], cocaine use, prior bleeding diverticuli, and chronic gout on 100 mg allopurinol PO daily who returned after d/c for diverticular bleed presents with pain and drainage from gouty tophi w/ evidence of mild superficial cellulitis. He is on kelfex for cellulitis and prednisone for acute gout flare. Wound cx + pansensitive MSSA. Blood cx neg. Ortho reconsulted 6/9 as questionable abscess requiring I&D. If no acute recommendations by ortho, pt stable for discharge to home.

Clinical Question: Would Febuxostat be a better medication than Allopurinol for management of gout in this patient with chronic kidney disease with a baseline creatinine of 2.7 mg/dl?

Search Strategy
Database: MEDLINE < 1950 to June Week 2 2009 >
1 Allopurinol/ 5785
2 Allopurinol/ and febuxostat.mp. and Gout/ 18
3 limit 3 to english language 16
4 Allopurinol/ and febuxostat.mp. and Gout/ 18 6 limit 5 to (english language and humans) 15

1) A critical reappraisal of allopurinol dosing, safety, and efficacy for hyperuricemia in gout. [Review] [36 refs]


3) Gout management: let's get it right this time.[comment]. Sundy JS. Arthritis & Rheumatism. 59(11):1535-7, 2008 Nov 15. [Comment. Editorial]

5) Refractory gout: what is it and what to do about it?. [Review] [45 refs]
Fels E. Sundy JS.
[Journal Article. Review]

6) Uricase and other novel agents for the management of patients with treatment-failure gout.
[Review] [38 refs]
Sundy JS. Hershfield MS.
Current Rheumatology Reports. 9(3):258-64, 2007 Jun.
[Journal Article. Research Support, Non-U.S. Gov't. Review]

7) Therapeutic advances in gout. [Review] [77 refs]
Pascual E. Sivera F.
[Journal Article. Review]

8) Febuxostat for prevention of gout attacks.
Pohar S. Murphy G.
[Journal Article]

9) Gout's not just for the gluttonous.
Anonymous.
[Journal Article]

10) Febuxostat versus allopurinol for gout.[comment].
Gelber AC.
[Comment. Letter]

11) Febuxostat versus allopurinol for gout.[comment].
Lustberg ME.
[Comment. Letter]

12) Febuxostat--treatment for hyperuricemia and gout?[comment].
Moreland LW.
[Comment. Editorial]

13) Febuxostat compared with allopurinol in patients with hyperuricemia and gout.[see comment].
Becker MA. Schumacher HR Jr. Wortmann RL. MacDonald PA. Eustace D. Palo WA. Streit J.
Joseph-Ridge N.
[Clinical Trial, Phase III. Comparative Study. Journal Article. Multicenter Study. Randomized Controlled Trial]
14) An update on the treatment options for gout and calcium pyrophosphate deposition. [Review] [100 refs]
Choy G.
[Journal Article. Review]

15) Serum uric acid-lowering therapies: where are we heading in management of hyperuricemia and the potential role of uricase. [Review] [79 refs]
Bomalaski JS, Clark MA.
Current Rheumatology Reports. 6(3):240-7, 2004 Jun.

COLUMBIA UNIVERSITY MEDICAL CENTER
DIVISION OF GENERAL MEDICINE

Senior Medicine Rotation: Based Medicine Project (Cont)

<table>
<thead>
<tr>
<th>Group</th>
<th>Criteria or definition</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population screened.</td>
<td>167 sites in the US mostly primary care</td>
<td>Unknown</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>18-85 years of age, with gout defined by American College of Rheumatology, hyperuricemia with serum urate level &gt;= 8 mg/dl, normal renal function (CR&lt;=1.5 mg/dl) or impaired renal function (CR&gt;1.5 -2 mg/dl)</td>
<td>1641</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>Intolerance to allopurinol, naproxen, colchicines; history of renal calculi; alcohol intake &gt;= 14 drinks/week, hepatic dysfunction with AST or ALT &gt;1.5 x upper limit, any other significant medical conditions.</td>
<td>1072</td>
</tr>
<tr>
<td>Treatment group</td>
<td>Febuxostat 80mg, 120mg, 240mg, and Allopurinol</td>
<td>938</td>
</tr>
<tr>
<td>No treatment group</td>
<td>Placebo</td>
<td>134</td>
</tr>
</tbody>
</table>

Primary endpoints: Proportion of subjects with the last 3 monthly serum urate levels < 6.0 mg/dl

Secondary endpoints:
- Proportion of subjects with a serum urate level <6 mg/dl at each visit
- Percent reduction of serum urate from baseline at each visit
- Proportion of subjects requiring treatment for a self reported gout flare between weeks 8 and 28
- Reduction in the number of tophi at each visit for subjects with palpable tophi at baseline
- Percent reduction in primary tophus size at each visit in the subjects with a primary palpable tophus at baseline.

- Are the Results of the Trial Valid?
  - Randomized?  Yes
  - All patients accounted for at end?  Yes
  - Intention to treat?  Yes
  - Blinding?  Yes
  - Groups similar at start of trial?  Yes
  - Equal treatment of groups?  Yes
  - Did randomization work?  Yes

- Are the Results of the Trial important?

<p>| Endpoint                      | Result               | Significance | ARR | NNT |</p>
<table>
<thead>
<tr>
<th>Morbidity</th>
<th>Result</th>
<th>Significance</th>
<th>ARI</th>
<th>NNH</th>
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</thead>
<tbody>
<tr>
<td>Serious adverse events</td>
<td>Treatment vs. Placebo</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Feb [80] 4% vs. 1%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Feb [120] 9% vs. 1%</td>
<td></td>
<td></td>
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<tr>
<td>Feb [240] 5% vs. 1%</td>
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</tr>
<tr>
<td>Allopur 7% vs. 1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Adverse events leading to withdrawal</td>
<td>Treatment vs. Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feb [80] 1% vs. 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feb [120] 2% vs. 0%</td>
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<tr>
<td>Feb [240] 0% vs. 0%</td>
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</tr>
<tr>
<td>Allopur 0% vs. 0%</td>
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</table>

- Can I apply these results to my patient?
  - Comparison of my patient to trial patients.
While this patient falls within the age, liver function, and alcohol restrictions, this patient has CR= 2.7 mg/dl and multiple other significant medical conditions such as CAD, HTN, CKD, MGUS, EtOH abuse [1/5 of liquor per week], and diverticulosis.

- All clinically important outcomes considered.
Yes, all important outcomes considered in the endpoints or adverse events.

- Likely benefits outweigh potential harms and cost?

No, while this study demonstrates a febuxostat is more effective in lowering serum urate concentration, within the 28 week study duration there was no significant decrease in clinical gout flares. A 3 year retrospective study by Shoji showed that a reduction of serum urate to <= 6.0 mg/dl eventually resulted in a reduced incidence of gout flares gives reason to suggest that a longer study may demonstrate benefit in clinical gout manifestations.

Most importantly this patient’s renal failure is more severe than the patients studied here and there is no study that evaluates febuxostat in patients with creatinine above 2 mg/dl. Although febuxostat is metabolized in the liver, fifty percent of the unchanged drug or its metabolites are excreted in the urine. In addition, this patient has multiple significant medical problems that may predispose him to adverse events secondary to the drug. Further study in patients with severe renal failure would be needed before I would recommend this to this patient.