COLUMBIA UNIVERSITY MEDICAL CENTER

DIVISION OF GENERAL MEDICINE

Senior Medicine Rotation: Evidence-Based Medicine Project

Resident Name: Aileen Chang Block: Senior Medicine Date: 6/20/09

Case SIGNOUT:

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\

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2) Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial.
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[Clinical Trial, Phase III. Journal Article. Multicenter Study. Randomized Controlled Trial. Research Support, Non-U.S. Gov't]

3) Gout management: let's get it right this time.[comment].
Sundy JS.
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4) Determinants of the clinical outcomes of gout during the first year of urate-lowering therapy.
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5) Refractory gout: what is it and what to do about it?. [Review] [45 refs]
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6) Uricase and other novel agents for the management of patients with treatment-failure gout. [Review] [38 refs]
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7) Therapeutic advances in gout. [Review] [77 refs]
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8) Febuxostat for prevention of gout attacks.
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Issues in Emerging Health Technologies. (87):1-4, 2006 Aug.
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9) Gout's not just for the gluttonous.
Anonymous.
Johns Hopkins Medical Letter, Health After 50. 18(4):3, 7, 2006 Jun.
[Journal Article]

10) Febuxostat versus allopurinol for gout.[comment].
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12) Febuxostat--treatment for hyperuricemia and gout?[comment].
Moreland LW.
New England Journal of Medicine. 353(23):2505-7, 2005 Dec 8.
[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.
New England Journal of Medicine. 353(23):2450-61, 2005 Dec 8.
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14) An update on the treatment options for gout and calcium pyrophosphate deposition. [Review] [100 refs]
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Expert Opinion on Pharmacotherapy. 6(14):2443-53, 2005 Nov.
[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]
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Senior Medicine Rotation: Based Medicine Project (Cont)

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

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?

Endpoint	Result	Significance	ARR	NNT
Proportion of subjects with	Treatment vs. Placebo			

the last 3 monthly serum urate levels < 6.0 mg/dl	Feb [80] 48% vs. 0% Feb [120] 65% vs. 0% Feb [240] 69% vs. 0% Allopur 22% vs. 0%	P< .001 P< .001 P< .001 P< .001		
Proportion of subjects with a serum urate level <6 mg/dl at each visit	Treatment vs. Placebo At Week 28 Feb [80] 76% vs. 1% Feb [120] 87% vs. 1% Feb [240] 94% vs. 1% Allopur 41% vs. 1% Treatment vs. Placebo At Final Visit Feb [80] 72% vs. 1% Feb [120] 79% vs. 1% Feb [240] 92% vs. 1% Allopur 39% vs. 1%	 P< .05 P< .05 P< .05 P< .05 P< .05 P< .05 P< .05 P< .05		
Percent reduction of serum urate from baseline at each visit	Treatment vs. Placebo At Week 28 Feb [80] 48% vs. 4% Feb [120] 55% vs. 4% Feb [240] 68% vs. 4% Allopur 34% vs. 4% Treatment vs. Placebo At Final Visit Feb [80] 45% vs. 3% Feb [120] 52% vs. 3% Feb [240] 66% vs. 3% Allopur 34% vs. 3%	 P< .05 P< .05 P< .05 P< .05 P< .05 P< .05 P< .05 P< .05		
Proportion of subjects requiring treatment for a self reported gout flare between weeks 8 and 28		No significant difference observed		
Total number and size of tophi		No significant difference observed		
Morbidity	**Result**	**Significance**	**ARI**	**NNH**
Serious adverse events	Treatment vs. Placebo Feb [80] 4% vs. 1% Feb [120] 9% vs. 1% Feb [240] 5% vs. 1% Allopur 7% vs. 1%	No significant difference observed		
Adverse events leading to withdrawal	Treatment vs. Placebo Feb [80] 1% vs. 0% Feb [120] 2% vs. 0% Feb [240] 0% vs. 0% Allopur 0% vs. 0%	No significant difference observed		

- 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.