Hyperuricemia and Gout an Update on Management

BY
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CATALINA POINTE ARTHRITIS AND RHEUMATOLOGY SPECIALISTS IN AUTOIMMUNE DISEASES, PC

Goal(s) of treating gout include?

- 1. Maintaining Serum Urate level < 6.0 mg/dl
- 2. Limiting acute flares of gout
- 3. Lowering total body stores or uric acid
- Preventing destructive arthritis due to uric acid deposition in joints
- 4. All of the above

The maximum dose of Allopurinol is?

- 1. 300 mg / day
- 2. 800 mg/day
- 3. What ever it takes to get urate < 6 mg/dl
- 4. Variable depending on renal function and side effects
- 5. combination of above options

Medications that inhibit uric acid production include?

1. Allopurionol (Zyloprim)
2. Febuxistat (Uloric)
3. Probenecid
4. Colchicine
5. 1 & 2

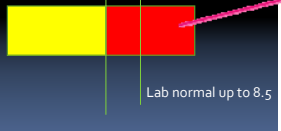
Should we be treating asymptomatic hyperuricemia?

1. Yes
2. No
3. Uncertain

Physiologic Urate level

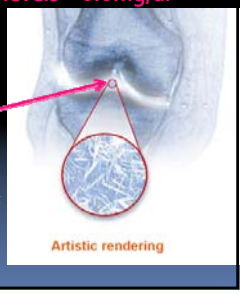
Urate saturation level= 6.8 mg/dl at 37 deg C

Physiiologic
< 6.8mg/dl at
temp < 37 deg C



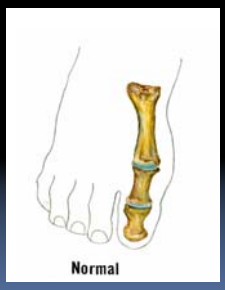
Lab normal up to 8.5

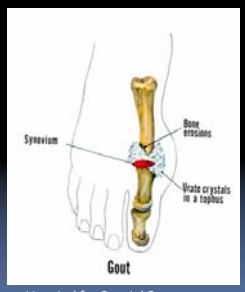
Urate → Uric acid at levels > 6.8mg/dl



Artistic rendering

Arthritic Complication of hyperuricemia → gout





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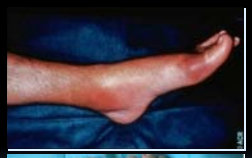
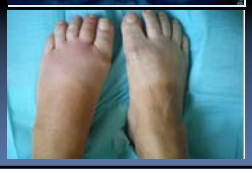
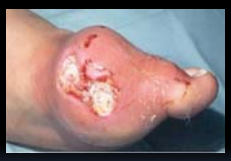
Clinical Manifestations of gout

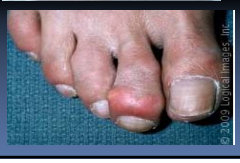
Acute Manifestations



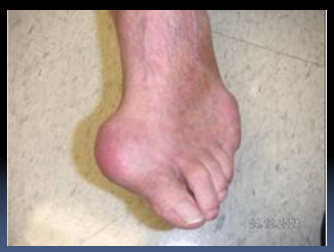


Chronic Manifestations





Podagra w/ Tophus



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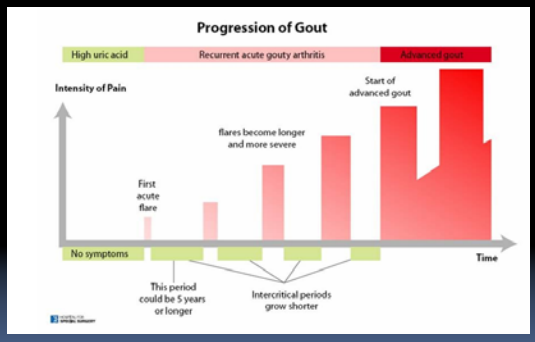

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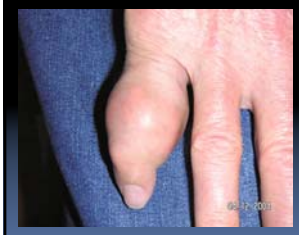
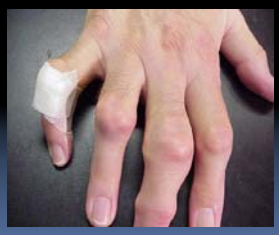
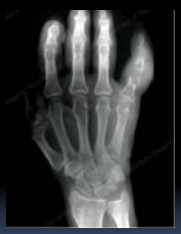
Clinical Manifestations of gout

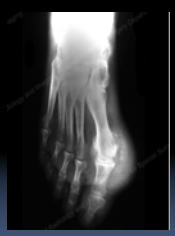
Tophi of the hands

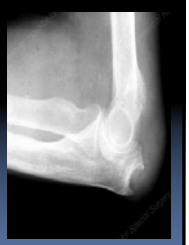




Gout: Radiographic changes

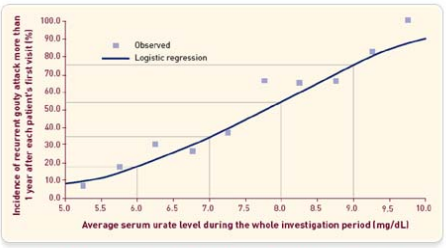






Fields NY.NY

Urate level and gout flares

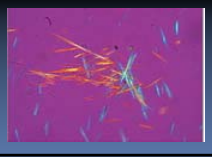


Based on a retrospective analysis of 267 gout patients for up to 3 years. Tokyo, Japan.

From Shoji A, Yamanaka H, Kamatani N. A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. *Arthritis Rheum*. 2004;51:321-325.

Diagnosing gout

Crystal proven



Not crystal proven

- Clinical presentation
- Uric acid > 6.8 mg/dl **not during an acute attack**
- Tophi present
- Above w/ classic radiographic changes
- Risk Factors
  - Family History
  - Diet / Beer intake

Diet and Gout

Low Purine Diet

- Beer
- Red Meat
- Organ meat
- Shell Fish
- Other

Enhancing urate excretion

- Vitamin C ?
- Cherry juice ?

Vitamin C and Gout

Compared to men w/ Vitamin C < 250mg /dl	Relative Risk Gout	95% Conf Intervals	P Value
Vitamin C 500-999 mg/dl	0.83	0.71-0.97	
Vitamin C 1,000 – 1499 mg/dl	0.66	0.52-0.86	
Vitamin C > 1,500 mg/dl	0.55	0.38-0.80	P < 0.001 for trend

Vitamin C intake and the risk of gout in men: a prospective study.
Choi HK - *Arch Intern Med* - 9-MAR-2009; 169(5): 502-7
N=46,994 males followed for 20 years, 1317 incident gout cases, questionnairs

Treating gout

Acute Flares

- Anti-inflammatory medication :
  - Nsaids
  - Colchicine- not used much unless started soon after attack started
  - Steroids-
    - Oral
    - Injection
- Sufficient doses and duration to control full flare (10-14 days +)
- Analgesics

Preventing Acute Flares

- Anti-inflammatory medication :
  - Nsaids- low dose daily
  - Colchicine – 0.6mg bid, qd or qod depending on renal function
  - Steroids-
    - Low dose daily oral
- Start these at time of urate lowering medication
- Continue for minimum 6 mo

Treating Acute Flares

- **Nsaids** – any one will do
  - High enough dose
  - Long enough treatment
  - Limited in renal insufficiency, anti-coagulation , CHF etc
- **Colchicine**
  - NO LONGER 1 every hour until diarrhea
  - Rather – 1 bid to tid for several days then back to 1 bid
  - Better for long term inhibition against flares
- **Steroids**
  - Steroid taper or injection if just one joint

Long term control of disease

- Probenecid – enhances urate renal clearance
  - Bid to tid
  - Some drug interactions
  - Works best if urine alkaline
  - Not for hyper excreters (~ 10%)
- Allopurinol – purine analgog- zanthine oxidase inhibitor
  - Dose 1 -2 every day
  - Minimal drug interactions
  - No trouble w/ acid or alkaline urine
- Uloric- non purine analagog- zanthine oxidase inhibitor

When to initiate Urate Lowering therapy

- Some suggest after 1st attack
- Multiple attacks
- Tophi
- Destructive changes on radiographs
- Concomitant diseases

- Start once acute attack subsides

Urate lowering therapy: Follow up testing

- Recheck Urate level minimum 2 weeks – typically 1 mo
- Adjust medication dose to achieve urate level < 6 mg/dl
- Monitor urate level once or twice a year to assure compliance
- Monitor renal, LFTs, CBC once or twice yearly

- No need to stop therapy for flares

Losartan and uricosuric effects

- Losartan molecule (no metabolite) interferes w/ urate resorption in proximal tubule → enhanced urate excretion and lowers Serum UA [1,2, 3]
- LIFE study (Losartan Intervention for Endoint reduction in HTN) demonstrated that Serum uric acid was associated w/ CV events and that losartan had lower UA than atenolol and may have accounted for better CV results.[4]
- Other ARBs have not shown same effect on lowering SUA or increaseing excretion UA [5]

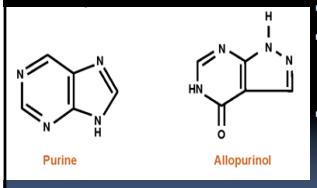
1. Nikas S. et al. J Renin Angiot Aldost Syst 2000;1
2. Soffer BA Hypertension 1995;26
3. Weber MA Arch Int Med 1995;155.
4. Hoieggen A Kidney Int 2004;65
5. Puig JG J Hypertens 1999;17

Fenofibrate and lowering uric acid

- Fenofibrate has been shown to increase uric acid excretion and lower serum uric acid and decrease episodes gout [1,2]
- Effect not seen w/ benzafibrate – thought therefore not to be the lipid lowering effect [3]
- Fenofibrate has been shown to enhance urate reduction in males treated w/ allopurinal [4,5]

1. Desager JP. J Clin Pharmacol 1980;20.
2. Hepburn AL Clin Rheum 2003;22.
3. Bastow MD Metabolism 1988;37
4. Feher MD. Rheumatology 2003;42.
5. Takahashi S Ann Rheum Ds 2003;62

Allopurinol- Xanthine Oxidase inhibitor



- Protein Binding < 1%
- 75% metabolized by liver to active metabolitye Oxypurinol
- Excretion : Urine 76% as Oxypurinol; 12% as unchanged drug

Allopurinol Renal Dose adjustments

Creatinine Clearance (mL/min) 1	Maintenance Dose of Allopurinol (mg) / day
140	400
120	350
100	300
80	250
60	200
40	150
20	100
10	100 every 2 days
0	100 every 3 days

[1]This table is based on a standard maintenance dose of 300 mg of allopurinol per day for a patient with a creatinine clearance of 100 mL/min. (Package Insert)

Advantages of Allopurinol

- Effective for both overproducers and underexcretors
- Convenience of single daily dose
- Can be efficacious in patients with renal insufficiency

Limitations of Allopurinol

- "Standard" doses may not achieve target serum urate
  - In one study, only 53% of allopurinol (300 mg qd) patients achieved target serum urate <6 mg/dL[1]
    - Higher doses were effective
- Need for dose adjustment according to renal function
  - Metabolites are excreted by the kidney. Accumulation can occur with renal insufficiency
- Precipitation of an acute attack
  - Lowering serum urate mobilizes deposited crystals

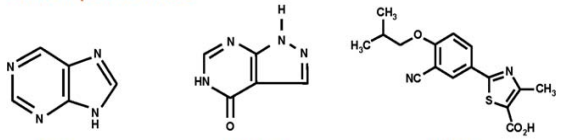
1. Perez-Ruiz. *Ann Rheum Dis*. 1998;57:545-549.

Limitations of Allopurinol

- Adverse effects
  - Rash
  - GI intolerance (diarrhea, nausea)
  - Increase in transaminases
  - Bone marrow suppression (uncommon)
  - Severe hypersensitivity syndrome
    - Occurs early in treatment
    - Infrequent, but life threatening (20% mortality)
    - Multi-symptom involvement – fever, rash, decreased renal function, vasculitis, hepatocellular injury, leukocytosis, and eosinophilia
    - Immediate drug withdrawal and supportive therapy

Febuxistat (Uloric)

- ULORIC has a nonpurine structure and is the first branded drug in 40 years for the treatment of hyperuricemia in gout patients
- ULORIC is not expected to inhibit other enzymes involved in purine/pyrimidine synthesis and metabolism at therapeutic doses



Purine Allopurinol ULORIC

Febuxistat (Uloric)

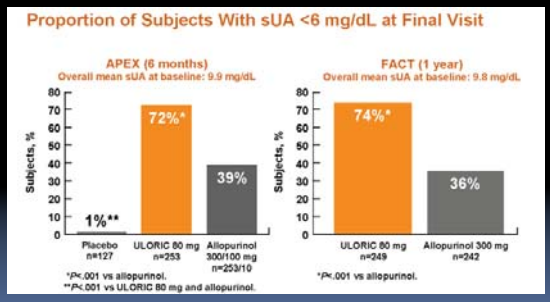
- Xanthine Oxudase Inhibitor
- Metabolized by liver
  - Glucaronidation
  - Cytochrome P450 (not 2D6)
- No drug interactions w/ Warfarin, Colchicine, Naproxen, Indomethacin, desipramine , HCTZ
- Excreted 45% feces; 49% inactive drug via kidney
- Only 3% unmetabolized drug excreted via kidney
- NO dose adjustment needed for renal insufficiency (creat. clearance ~ 30cc/min

Demographics for 3 phase 3 febuxistat trials

Male	95%
Race: Caucasian African American	80% 10%
Ethnicity: Hispanic or Latino	7%
Alcohol user	67%
Mild-to-moderate renal insufficiency (percent with estimated Cl_{Cr} <90 mL/min)	59%
History of hypertension	49%
History of hyperlipidemia	38%
BMI ≥30 kg/m^2	63%
Mean BMI	33 kg/m^2
Mean age	52
Mean baseline sUA	9.7 mg/dL
Experienced a gout flare in previous year	85%

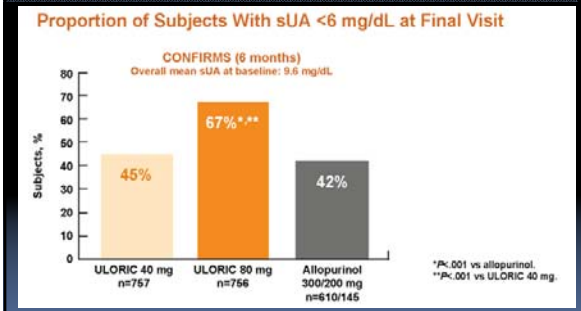
*In the phase 3 trials APEX, FACT, and CONFIRMS.

Febuxistat vs Allopurinol



Tekada Package insert

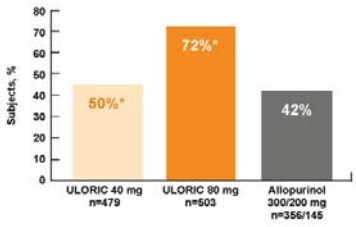
Febuxistat vs Allopurinol



Tekada Package insert

Febuxistat vs Allopurinol Renal Insufficiency patients

Proportion of Subjects With Mild-to-Moderate Renal Impairment With sUA <6 mg/dL at Final Visit



*P≤.05 vs allopurinol.
Renal impairment was defined as baseline estimated Cl_{Cr} ≥30 mL/min and <90 mL/min.

Tekada Package insert

Febuxistat vs Allopurinol: Adverse Reactions

Treatment-Related Adverse Reactions Occurring in ≥1% of ULORIC-Treated Subjects* in Phase 3 Controlled Studies

Adverse Reactions	Placebo (n=134)	ULORIC 40 mg daily (n=757)	ULORIC 80 mg daily (n=1279)	Allopurinol 300/200/100 mg daily (n=1277)
Liver Function Abnormalities	0.7%	6.6%	4.6%	4.2%
Nausea	0.7%	1.1%	1.3%	0.8%
Arthralgia	0%	1.1%	0.7%	0.7%
Rash	0.7%	0.5%	1.6%	1.6%

*At a ≥0.5% greater rate than with placebo.

Tekada Package insert

Febuxistat vs Allopurinol: Adverse Reactions

- During phase 3 studies, transaminase elevations greater than 3 times the upper limit of normal (ULN) were observed
- No dose-effect relationship for these elevations was noted

ALT and/or AST ≥3 × ULN	ULORIC	Allopurinol
AST	2%	2%
ALT	3%	2%

Tekada Package instrt

Febuxistat vs Allopurinol: Adverse Reactions

Incidence Rate of Adjudicated APTC Events per 100 Patient-Years of Exposure in ULORIC Clinical Trials

	Rate	95% CI
Phase 3 Randomized Controlled Studies		
Placebo	0.00	0.00-6.16
ULORIC 40 mg	0.00	0.00-1.08
ULORIC 80 mg	1.09	0.44-2.24
Allopurinol	0.60	0.16-1.53
Overall		
ULORIC	0.74	0.36-1.37
Allopurinol	0.60	0.16-1.53
Long-Term Extension Studies		
ULORIC 80 mg	0.97	0.57-1.56
Allopurinol	0.58	0.02-3.24

APTC=Antiplatelet Trialists' Collaboration, CI=confidence interval.

Febuxistat vs Allopurinol: Adverse Reactions

Cardiovascular Events: In randomized controlled studies, there was a higher rate of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) in patients treated with ULORIC [0.74 per 100 P-Y (95% CI 0.36-1.37)] than allopurinol [0.60 per 100 P-Y (95% CI 0.16-1.53)]. A causal relationship with ULORIC has not been established. Monitor for signs and symptoms of MI and stroke.

The Future of the Treatment of Hyperuricemia: Uricase Enzymes

- Uricase enzymes further catabolize uric acid to a more soluble, readily excretable form
- Agents available
  - Include rasburicase and aspergillus uricase (ex-US)
  - PEGylated recombinant uricases in phase II clinical trials
    - Polyethylene glycol (PEG) modification reduces antigenicity and prolongs half-life

Pay et al. *Curr Rheumatol Rep*. 2003;5(3):213-214.
http://www.phoenixpharm.org/products/uricasepeg20.htm.

The Future of the Treatment of Hyperuricemia: Uricase Enzymes

- Rasburicase
  - Not indicated for hyperuricemia of gout
    - Indicated for management of hyperuricemia in tumor lysis syndrome of pediatric oncology[1]
  - Studies show dramatic reductions in uric acid levels[1]
  - Potential for immunogenicity and subsequent fatalities

Black box warnings for anaphylaxis, hemolysis, and methemoglobinemia[2]

1. Coiffier et al. *J Clin Oncol*. 2003;21(23):4402-4406.
2. Elitek Package Insert. Sanofi-Synethlabo Inc. 2001.

Controversies related to gout/hyperuricemia

- Should asymptomatic hyperuricemia be treated?
- Is there a physiologic relationship between hyperuricmeia and HTN?
- Is hyperuricemia an inocent bystander of an independent predictor of ASCAD and mortality?

Co-morbidities Associated With Hyperuricemia

- Obesity[1,2]
- Metabolic syndrome[3]
- Diabetes mellitus[4]
- Heart failure[5]
- Hyperlipidemia[1]
- Hypertension[6,7]

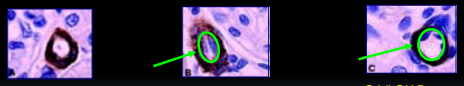
1. Nakanishi et al. *Int J Epidemiol*. 1999;28(5):888-893.
2. Denzer et al. *J Ped Endo Met*. 2003;16:1225-1232.
3. Ford et al. *JAMA*. 2002;287:356-359.
4. Boyko et al. *Diabetes Care*. 2000;23(9):1242-1248.
5. Anker et al. *Circulation*. 2003;107:1991-1997.
6. Gavin et al. *Am J Cardiovasc Drugs*. 2003;3(5):309-314.
7. Feig et al. *Hypertension*. 2003;42:247-252.

Hyperuricemia & Hypertension
A Potential Explanation of Association
(cont'd)

- Effects on the afferent arteriole after 5 weeks

Uncontrolled hyperuricemia: Arteriole thicker, lumen smaller

Controlled hyperuricemia: Arteriole thinner, lumen larger



Control group | OA/LS group | OA/LS/AP group

- Association to glomerular hypertension may be caused by afferent arteriole thickening
  - Suggestive of hypertrophic vascular remodeling

Sanchez-Lozada et al. *Am J Physiol Renal Physiol.* 2002;283:F1105-F1110.

Studies w/ significant association between high uric acid preceding HTN and found to be independent predictor

- Bogalusa Hrt Study n=550 children 12yr f/u Alper AB Hypertens 2005;45:34-38
- Kaiser Permanete Medical Care Program n=1031 RR 2.19 Selby JV. Am J Epidemiol 1990;131:1017-27
- Utah HTN Screening n=1482 . RR 2.06 Hunt CS. Hypertens 1991;17:969-76
- Olivetti Heart Study. n=619 Italian men. RR 1.23 Jossa F J. Hum Hypertens 1994;8:677-81
- Osaka Health Survey n= 6356 Japanese males RR 2.01. Taniguchi Y. J Hypertens 2001;19:1209-15

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- 2. Limiting acute flares of gout
- 3. Lowering total body stores or uric acid
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