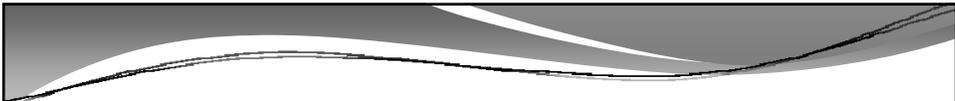


# **RECENT ADVANCES IN THE PATHOGENESIS AND TREATMENT OF GOUT**

Vincent J. Giuliano MD, FACP, FACR  
Professor of Medicine  
Division of Clinical Rheumatology  
University of Virginia



## **DISCLOSURES**

NONE

## OBJECTIVES

- To understand the latest concepts on the pathogenesis of hyperuricemia and gout
- To review the most effective ways to administer medicines for prophylaxis and treatment of acute gout
- To explore the use of Pegloticase in the treatment of chronic tophaceous gout

## EPIDEMIOLOGY OF ACUTE GOUT

- Gout affects 1% of the U.S. adult population. It is the most common inflammatory disease in the elderly, affecting especially males between ages 75-84.
- Annual incidence of gout increases with increasing hyperuricemia.
  - If uric acid is 7.0-8.9 mg/dl, incidence is 0.5%
  - If uric acid is 9.0 or above, incidence increases to 4.5%
- **HYPERURICEMIA IS NOT THE SAME AS GOUT!**

## HYPERURICEMIA

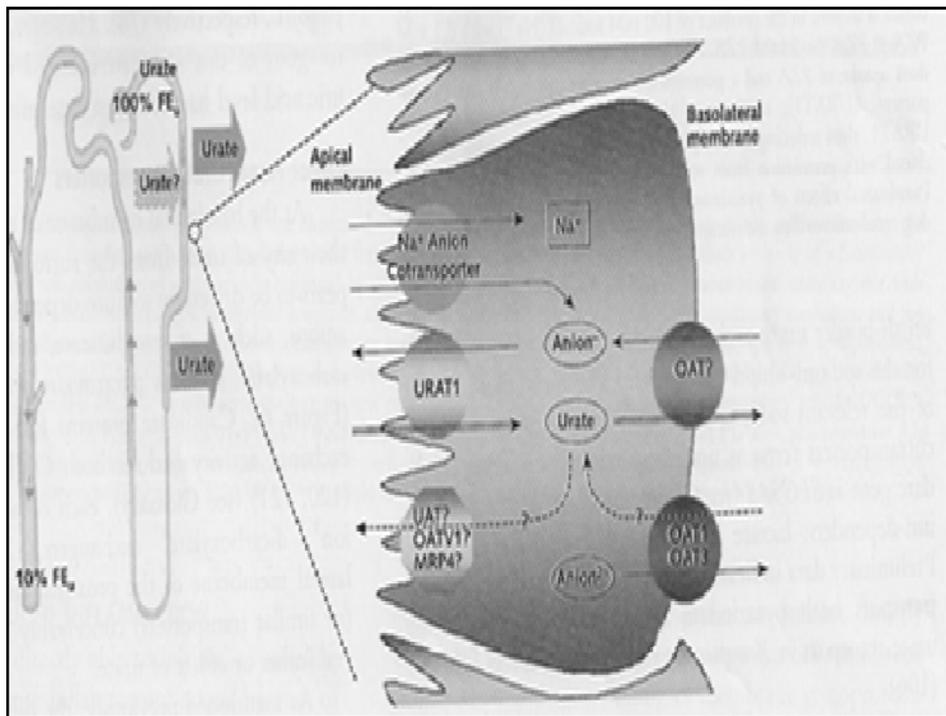
- The solubility of uric acid in plasma reaches the saturation point at 6.8 mg/dl when pH is 7.4 and temperature is 37°. Levels above that are supersaturated and are prone to crystallization.
- There is a strong association of hyperuricemia with diabetes, hypertriglyceridemia and hypertension.
- Alcohol consumption is directly correlated with urate concentrations, mainly due to increased urate reabsorption from the kidney. Additionally, beer contains the purine base, guanadine, adding to the purine load.
- Uric acid kidney stones are less common than gout at comparable serum concentrations of uric acid.

## HYPERURICEMIA AND THE METABOLIC SYNDROME

- Hyperuricemia closely correlates with the degree of insulin resistance and the development of Type 2 diabetes.
- High levels of dietary fructose may play a role in that it is the only sugar that directly elevates uric acid levels through intracellular phosphate depletion and stimulation of AMP deaminase leading to de novo urate synthesis.
- Debate persists on the degree of cardiovascular risk attributable to elevated uric acid alone as opposed to the effects of hyperuricemia on the kidney leading to hypertension.

## RENAL CLEARANCE OF URIC ACID

- The kidney accounts for 60% of the daily elimination of uric acid, the rest being excreted through the GI tract.
- The pKa of uric acid is 5.35 leading to it being partially ionized in urine with a pH of 5.5-7.0. At pH 7.4 it is 98% ionized and readily forms a soluble sodium salt, monosodium urate.
- On the apical side of the proximal tubular epithelium (luminal side) are found organic acid transporters (OAT) which exchange intracellular anions such as lactate, acetoacetate, etc. for extracellular anions such as urate.
- The most specific OAT for urates is URAT1 (urate/anion transporter) which exchanges luminal urates for intracellular organic acids leading to urate reabsorption.
- The energy for this exchange is a  $\text{Na}^+/\text{K}^+$ -ATPase pump on the basolateral surface of the epithelial cell



## CLINICAL ASPECTS OF RENAL

### URATE CLEARANCE

Some drugs including probenecid, sulfinpyrazone and losartan which can serve as substrates for the antiporter activity of URAT<sub>1</sub> (cis inhibition) thus serving as uricosuric agents

- Intracellular accumulation of organic acids such as lactate, nicotinate and hydroxybutyrate increases urate reabsorption through URAT<sub>1</sub> (trans stimulation). This is the probable mechanism for hyperuricemia secondary to alcohol ingestion and taking niacin.
- Excessive reabsorption of uric acid by the kidney accounts for 90% of hyperuricemia.
- Some genes for encoding OAT's have been identified and may be responsible for development of primary hyperuricemia, as well as hypouricemia.

## PATHOGENESIS OF THE ACUTE

### ATTACK OF GOUT

Sudden changes in concentration can lead to remodeling of articular urate crystal deposits. This can occur in states of :

- Lowering of the pH as in metabolic acidosis, which also leads to increased tubular reabsorption as well as decreased urate solubility.
- Lowering of the temperature, and, thus, the solubility, which may explain the prevalence of gout in the first MTP joint.
- Increased UA reabsorption due to alcohol ingestion
- Increased UA concentration secondary to ingestion of purines, e.g. shellfish, meats and beer.
- Increase in fatty acids in plasma which act as a cofactor for inflammasome stimulation.
- Beginning a uric acid lowering drug.

## TREATMENT OF ACUTE AND CHRONIC GOUT

1. Terminate the acute attack
2. Determine factors causing attack
3. Decide on appropriate prophylaxis for future attacks
4. Decide on need for uric acid lowering medication

## TERMINATION OF ACUTE GOUT

- COLCHICINE - Previous regimen of hourly colchicine is no longer recommended. If begun within the first 12 hours, giving 1.2 mg of colchicine followed by 0.6 mg one hour later is as effective as previous regimen with much less GI toxicity.
- NSAIDS - Maximum doses of NSAID should be given in the first 24 hours, e.g. piroxicam 40 mg then 20mg 12 hours later, followed by 20 mg for 7-10 days.
- CORTICOSTEROIDS - given orally or parentally is a good substitute for NSAID. 30 mg daily for 5 days is a common regimen. Is also effective as an intra-articular injection in post operative patients.

## IL-1 $\beta$ INHIBITION AS A TREATMENT FOR GOUT

- Production of IL-1 $\beta$  by inflammasomes in macrophages is a major contributor to inflammation.
- Colchicine inhibits the enzyme caspase 1 necessary to transform pro IL-1 $\beta$  to IL-1 $\beta$
- Anakinra blocks the IL1 receptor and has been used in acute gout (100mg sc. x 3-5 days)
- Canakinumab is an anti IL-1 $\beta$  antibody and has also been used in gout. It is only approved for Muckle-Wells syndrome

## DETERMINING FACTORS CAUSING THE ATTACK

- Determination of precipitating factors e.g. alcohol intake, high purine meal, should be done prior to deciding about urate lowering medication.
- An investigation of causes of hyperuricemia should also be done evaluating for high purine turnover states e.g. psoriasis, hemaglobinopathy. Renal insufficiency, metabolic syndrome, diuretic use should be identified.

## URIC ACID LOWERING AGENTS

- XANTHINE OXIDASE INHIBITORS
  - Allopurinol
  - Febuxostat
- URICOSURIC AGENTS
  - Probenecid
- URICASE
  - Peg-uricase

## PROBLEMS WITH ALLOPURINOL USE

- 300mg/day often not enough. Dose can be increased to 600 mg/d with minimal increase in toxicity. Target is to get uric acid <6 mg/dl
- Allergic rash in 3-5%. Most frequent is LCV
- Rare severe hypersensitivity syndrome. This can lead to multi-organ failure, hepatitis and vasculitis with significant mortality. ( $\pm$  20%)
- Significant drug interactions
  - Azathioprine- reduce dose of allopurinol by 2/3
  - Cyclosporine- blocks renal clearance of allopurinol
  - Ampicillin- associated with rashes
- Non compliance – only 50% still taking it after 6 months. Can lead to inappropriate dosage increase.

## FEBUXOSTAT

- A non-purine xanthine oxidase inhibitor which is more selective than allopurinol.
- Not cross reactive with allopurinol, making it a good alternative in allopurinol allergic or intolerant patients.
- Dose of 80-120mg/d leads to reduction of uric acid levels in 90%. Can raise dose to 240mg/d. In patients with UA >10mg/dl, it is superior to allopurinol in reaching target of 6mg/dl.
- Mainly cleared by liver so may be safer in renal insufficiency. Is contraindicated in patients taking azathioprine, 6MP, and theophylline.
- Main adverse effects are elevated LFTs and rashes.

## PROPHYLAXIS AGAINST FUTURE ATTACKS OF GOUT

- COLCHICINE – remains the preferred prophylactic agent. Usually a dose of 0.6mg daily is sufficient. Can give bid if CrCL>60ml/min
- NSAIDS – can also be used instead of colchicine if former isn't tolerated.
- Renal insufficiency may preclude use of either of the above. Corticosteroids e.g. prednisone 5mg/day is an alternative.
- Removal of precipitating agents e.g. alcohol binges, especially beer which is high in guanidine, diuretic agents, high fructose foods.
- Adding losartan for blood pressure control as it is a URAT<sub>1</sub> inhibitor.

## TREATMENT OF ADVANCED TOPHACEOUS GOUT



## PEGLOTICASE

- IV uricase has been used in the past to reduce uric acid levels in the tumor lysis syndrome. Antigenicity limits its repeated use.
- PEGylation of uricase reduces its antigenicity and prolongs the half life. It works better IV than SC.
- Indications are for chronic gout refractory to maximal doses of xanthine oxidase inhibitors. It can also be used for reduction of tophaceous deposits.
- Usual dose is 8mg IV infusion over 2 hours. Uric acid levels fall markedly down to 1-2mg/dl within 72 hours and should maintain level <5mg/dl until the next infusion.
- Contraindicated in patients with G6PD deficiency as this can precipitate hemolysis and methemoglobinemia.
- Uric acid lowering drugs and uricosurics should be stopped prior to giving PEG-uricase. Prophylactic colchicine or NSAID should be started at least a week prior to first infusion.

## TOXICITY OF PEGLOTICASE

- Serious infusion reactions including anaphylaxis can occur due to anti-pegloticase antibodies. These usually occur within 2 hours of the infusion.
- Antibodies develop in large majority of patients. High titers reduce the effectiveness, so a uric acid level should be checked prior to each infusion. Infusion should not be given if UA level is  $>6.0$
- Urate lowering drugs are to be stopped so that the UA level reflects the action of the pegloticase.
- Induction of gout flare after infusion is very common and gout prophylaxis needs to be started well before the first infusion.

## SUMMARY

- In the last few years, much has been added to our understanding of the mechanisms for developing hyperuricemia and induction of an acute attack of gout.
- This has led to the development of new therapeutic agents such as febuxostat, IL-1 $\beta$  inhibitors, and pegloticase.
- Evidence suggests that better control of hyperuricemia can be obtained with treatment of the metabolic syndrome and by adding losartan to the treatment of hypertension while restricting the use of thiazide diuretics.