Refractory Gout:
An overview of pathogenesis and treatment

Gordon K. Lam, MD, FACR

NorthEast Rheumatology
Medical Director, Northern Region Research Center
Carolinas Healthcare System

Disclosures

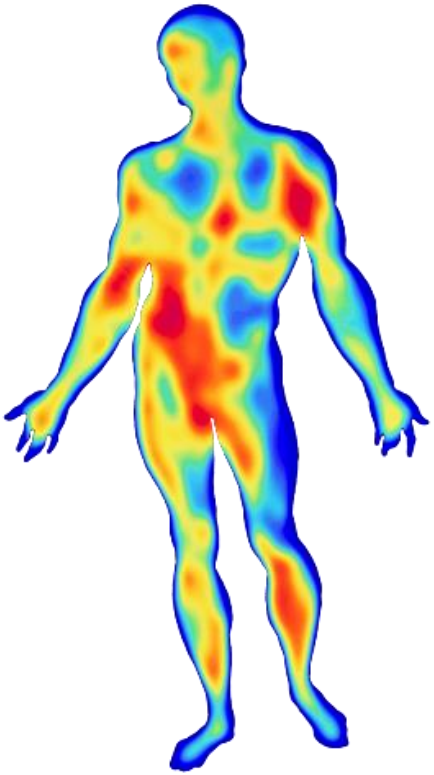
1. Horizon Pharma, Plc: Research; Speaker Bureau
2. Takeda Pharmaceuticals USA, Inc.: Speaker Bureau; Advisory Board

Objectives

- To review the etiopathogenesis of gout as a chronic, progressive, inflammatory arthritis
- To differentiate the treatment of acute gout flares vs. chronic gouty arthropathy
- To discuss the management of refractory gout
- To facilitate collaboration between podiatrists and rheumatologists in the management of gout patients

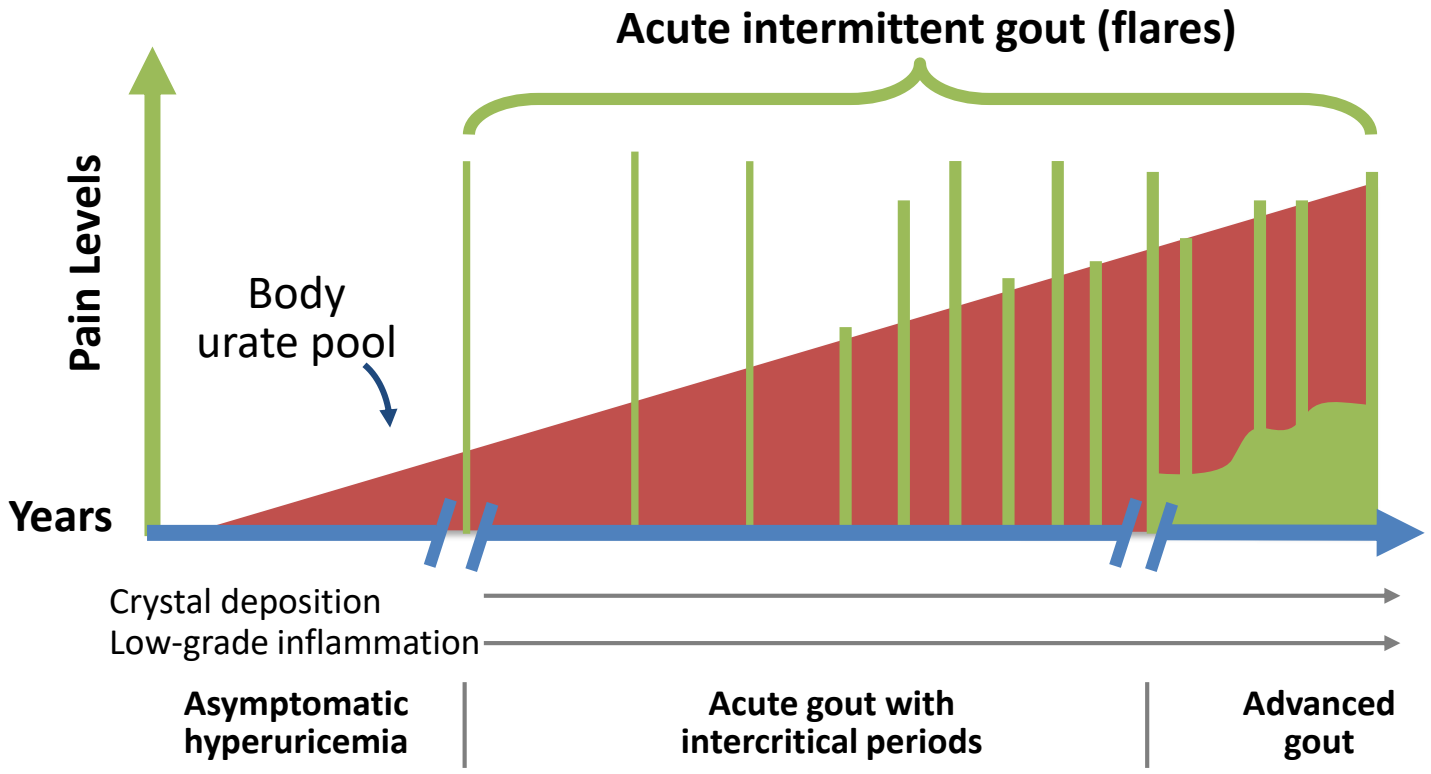
Gout definition

- An inflammatory arthritis caused by the deposition of monosodium urate (MSU) crystals in synovial fluid and other tissues
  - Crystal deposition occurs when serum uric acid (SUA) concentration exceeds its solubility
  - As gout progresses, crystal deposition can occur anywhere in the body
  - Chronic disease can lead to sequelae including:
    - Bone erosions
    - Tophi
    - Chronic pain
    - Joint deformities
    - Loss of function
    - Disability



Temperature	Calculated Urate Solubility (mg/dL)*
37°C (98.6°F)	6.8
35°C (95.0°F)	6.0
30°C (86.0°F)	4.5

Gout is a chronic, progressive disease

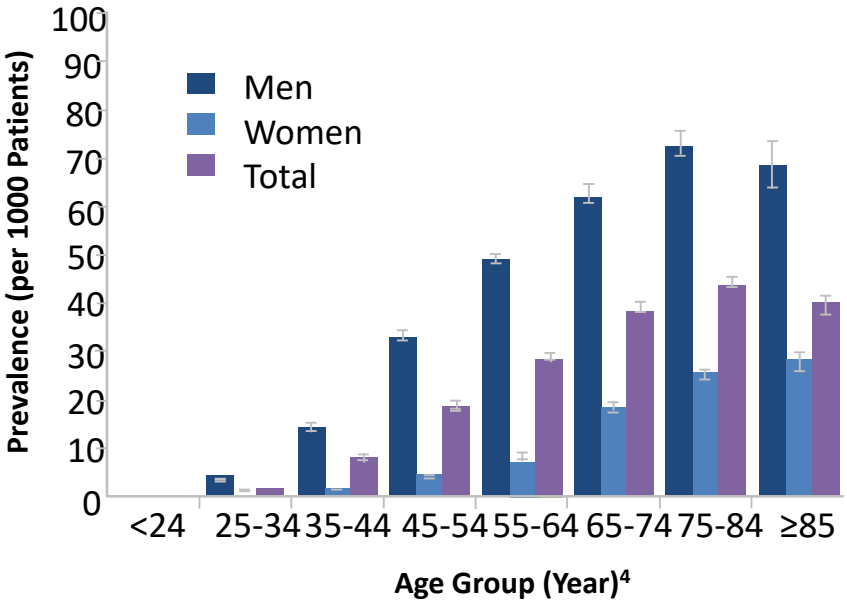


Subclinical inflammation may be present even in the intercritical periods

Adapted from Edwards NL. Gout. A. Clinical features. In: Klippel JH, Stone JH, Crofford LJ, White PH, eds. *Primer on the Rheumatic Diseases*. 13th ed. New York: Springer; 2008:241-249.

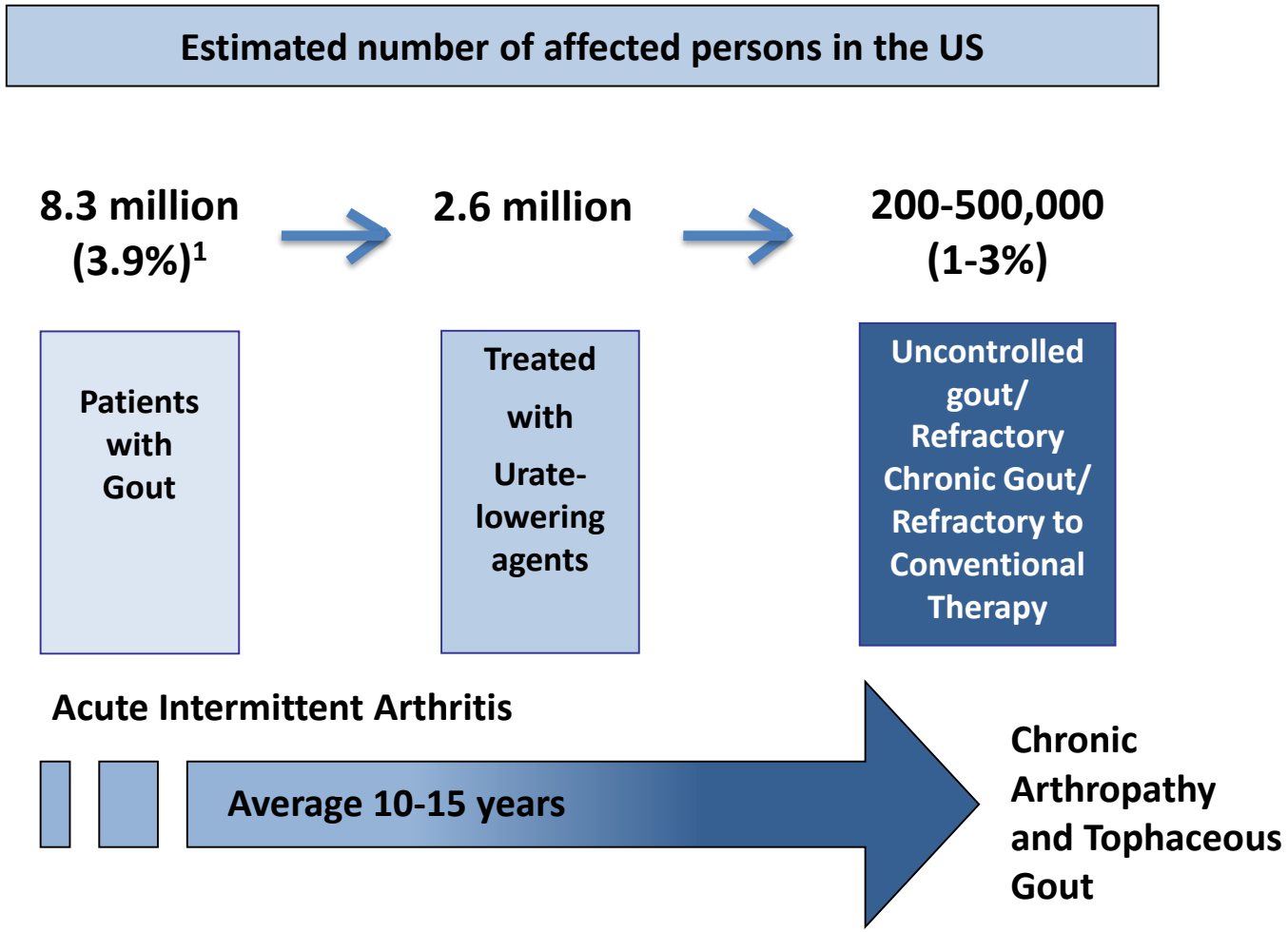
Prevalence

- Gout is the most common form of inflammatory arthritis
- Est. prevalence in U.S. 2007-2008: 3.9% (8.3 million)
- Prevalence is increasing worldwide
- Incidence is greater in men than in women
- Incidence increases with age
  - Mainly due to proportional decline in renal function
- Refractory gout estimated to be 2% of all gout patients



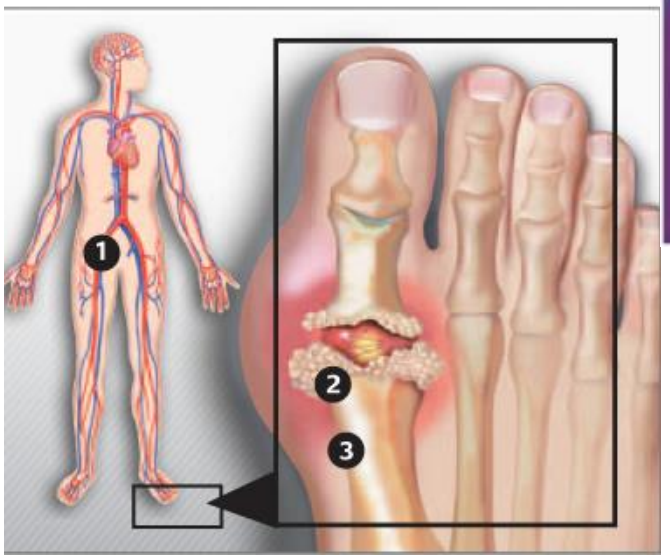
Reprinted from Mikuls TR et al. *Ann Rheum Dis*. 2005;64(2):267-272

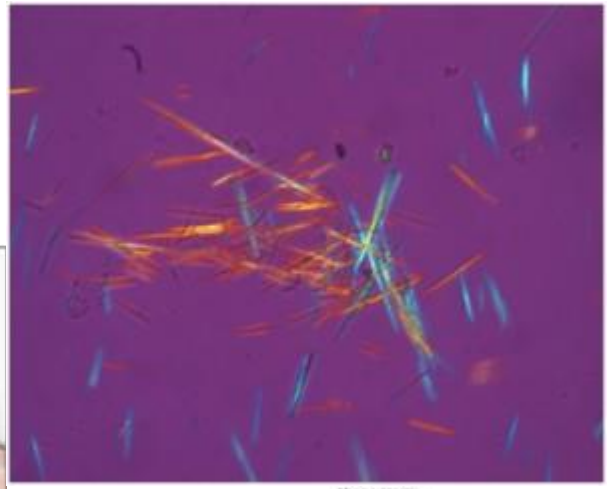
Spectrum of Gout

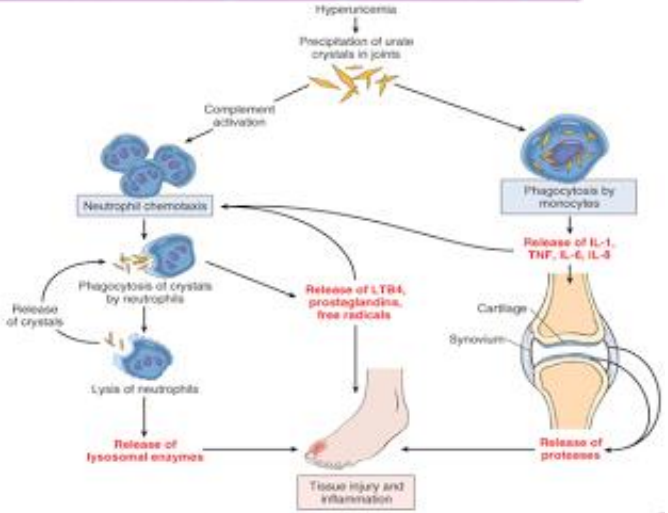


Zhy Y et al. Arthritis Rheum, 2011;63(10):3136-41.

Etiopathogenesis of Gout





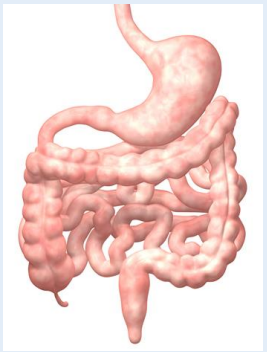


Pathogenesis of acute gouty arthritis

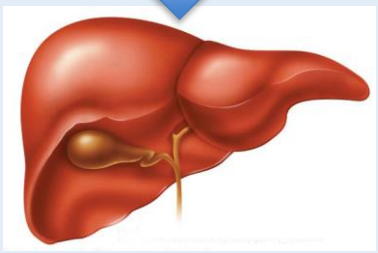
Regulation of uric acid

Normal Human Uric Acid Turnover

- Dietary intake

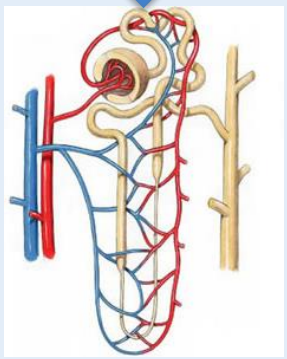


- Normal cellular degradation
- De novo purine synthesis
- Psoriasis
- Malignancy
- Tumor lysis syndrome



- Muscular exercise

- Purine catabolism in other organs (lungs, brain, etc.)



Excretion GI tract (25-33%)

Excretion Kidney (66-75%)

Causes of hyperuricemia

Under-excreters of urate (~90%)

Clinical Disorders

- Chronic renal failure
- Lead nephropathy
- Polycystic kidney disease
- Familial juvenile hyperuricemic nephropathy
- Medullary cystic kidney disease
- HTN
- Dehydration
- Salt restriction
- Starvation
- Diabetic ketoacidosis
- Lactic acidosis
- Obesity
- Hyperparathyroidism
- Hypothyroidism
- Diabetes insipidus
- Sarcoidosis
- Toxemia of pregnancy
- Bartter's syndrome
- Chronic beryllium disease
- Down syndrome

Drugs or Dietary Habits

- Diuretics
- Low doses of salicylates
- Ethambutol
- Pyrazinamide
- Laxative abuse (alkalosis)
- Levodopa
- Methoxyflurane
- Cyclosporine
- Tacrolimus

Overproducers of urate (~10%)

Inherited Enzyme Defects

- HPRT deficiency
- Increased PRPP synthetase
- Glucose 6 phosphatase deficiency (glycogenosis I)

Clinical Disorders Leading to Purine Overproduction

- Myeloproliferative disorders
- Lymphoproliferative disorders
- Polycythemia vera
- Malignant diseases
- Hemolytic disorders
- Psoriasis
- Obesity
- Tissue hypoxia
- Glycogenosis III, V, VII

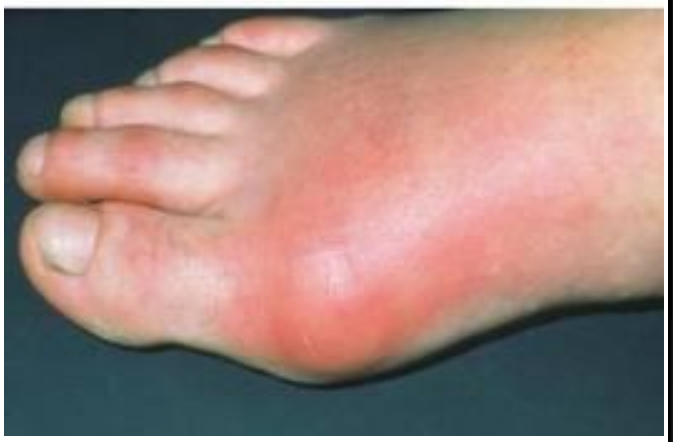
Drugs or Dietary Habits

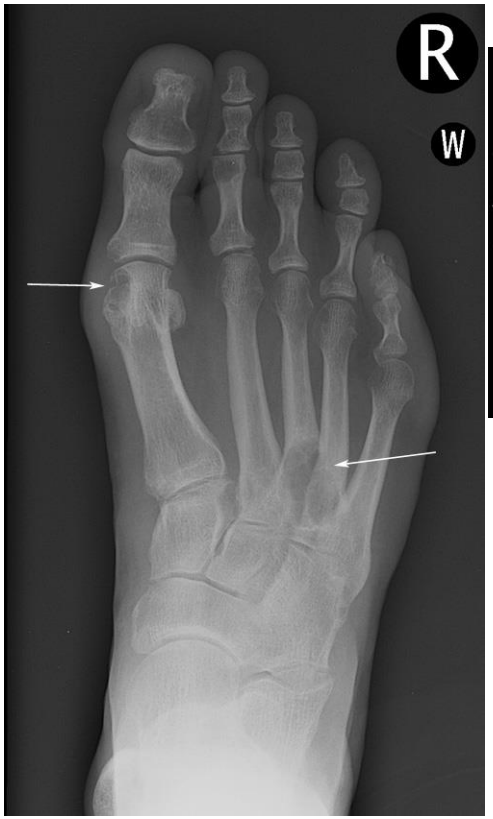
- Ethanol
- Diet rich in purines
- Pancreatic extract
- Fructose
- Nicotinic acid
- Ethylamino-1,3,4-thiadiazole
- 4-Amino-5-imidazole carboxamide riboside
- Vitamin B12 (patients with pernicious anemia)
- Cytotoxic drugs
- Warfarin

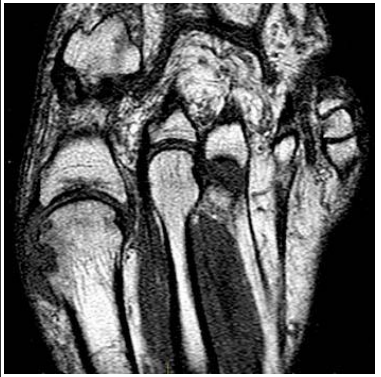
Becker MA, Jolly M. Clinical gout and the pathogenesis of hyperuricemia. In: Koopman WJ, Moreland, LW, eds. *Arthritis & Allied Conditions*. 15th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:chap 113.

Urate deposition in the body

Joints

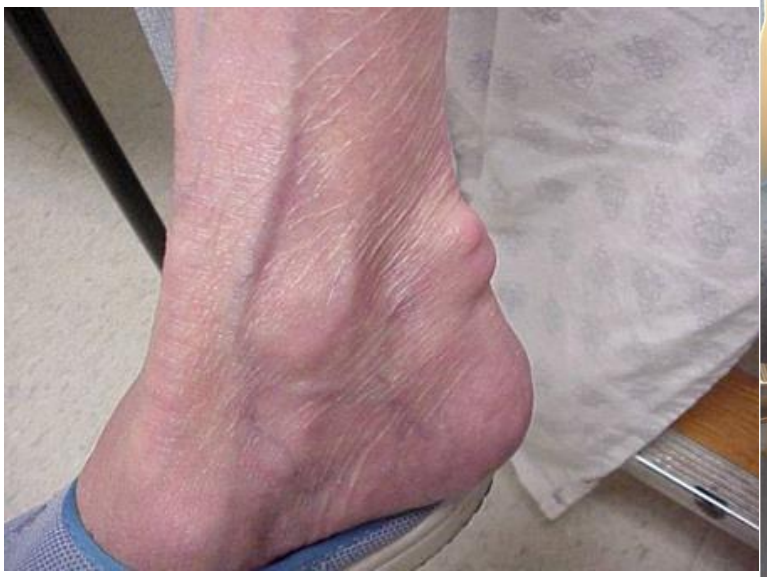


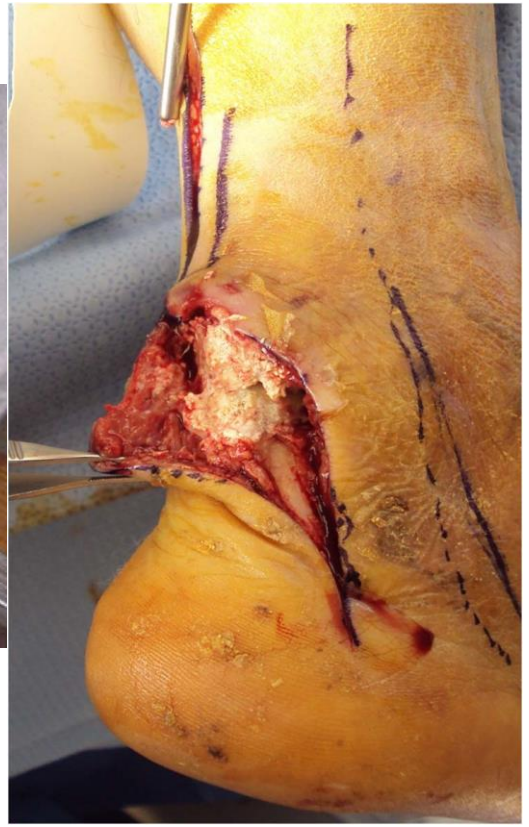




Urate deposition in the body

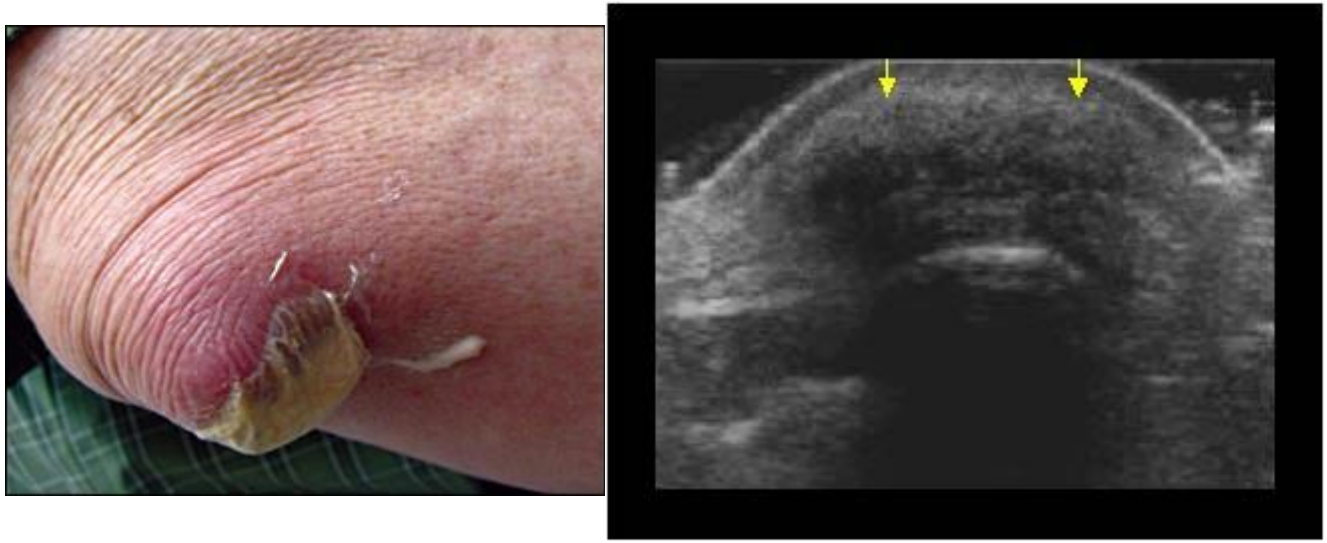
Tendons





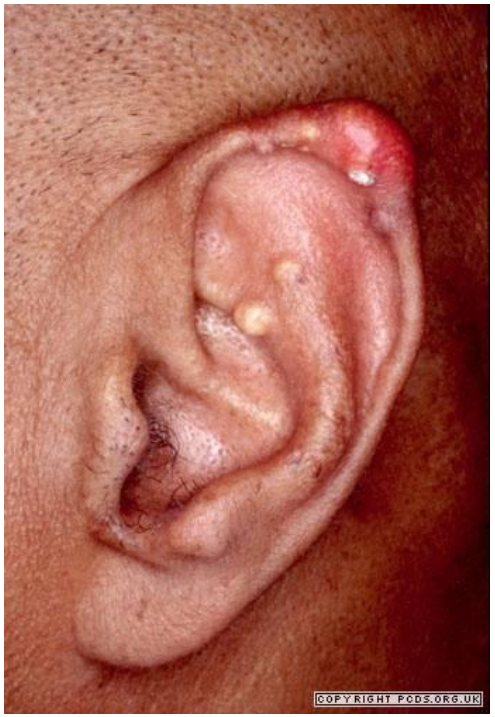
Urate deposition in the body

Bursae



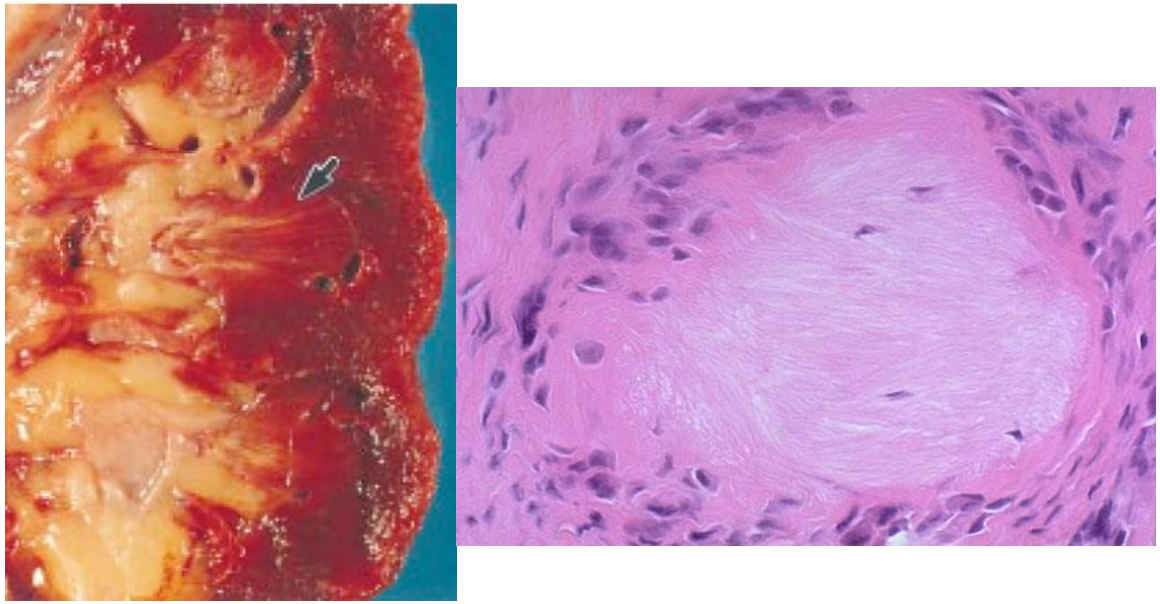
Urate deposition in the body

Ears



Urate deposition in the body

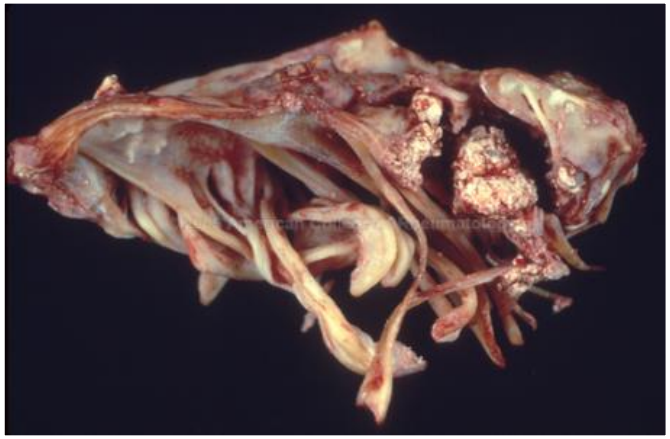
Kidneys



Urate deposition and fibrosis

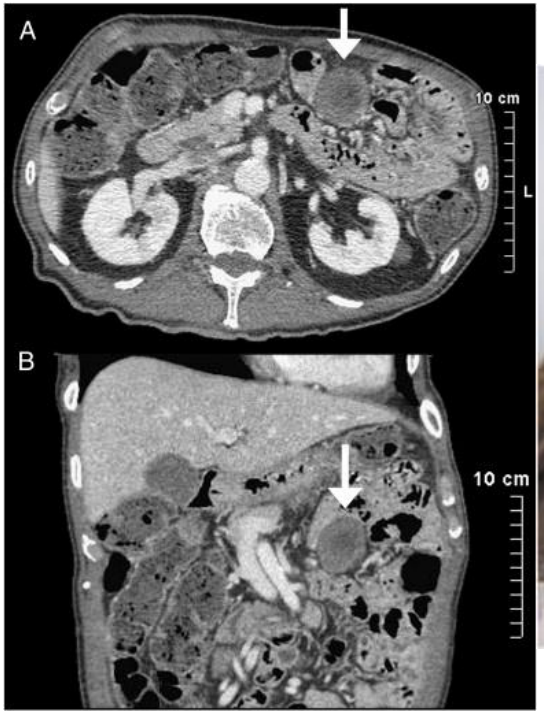
Urate deposition in the body

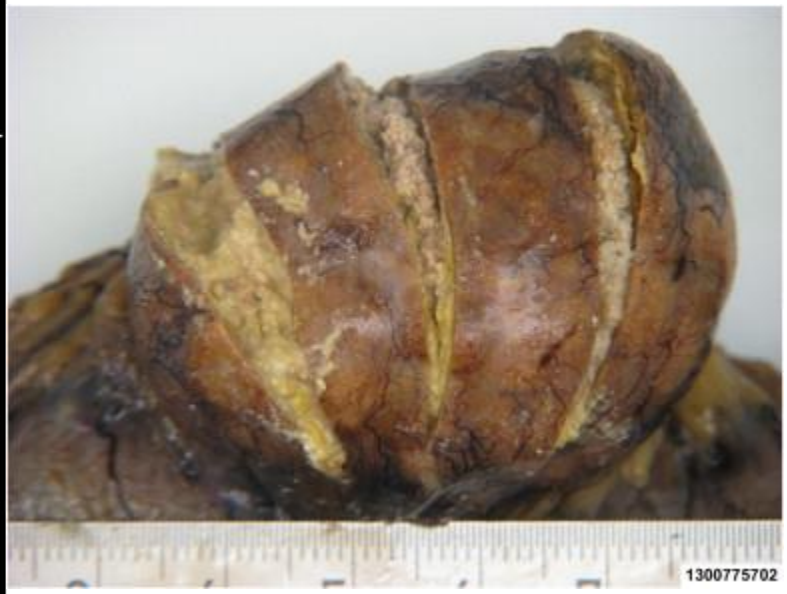
Mitral valve



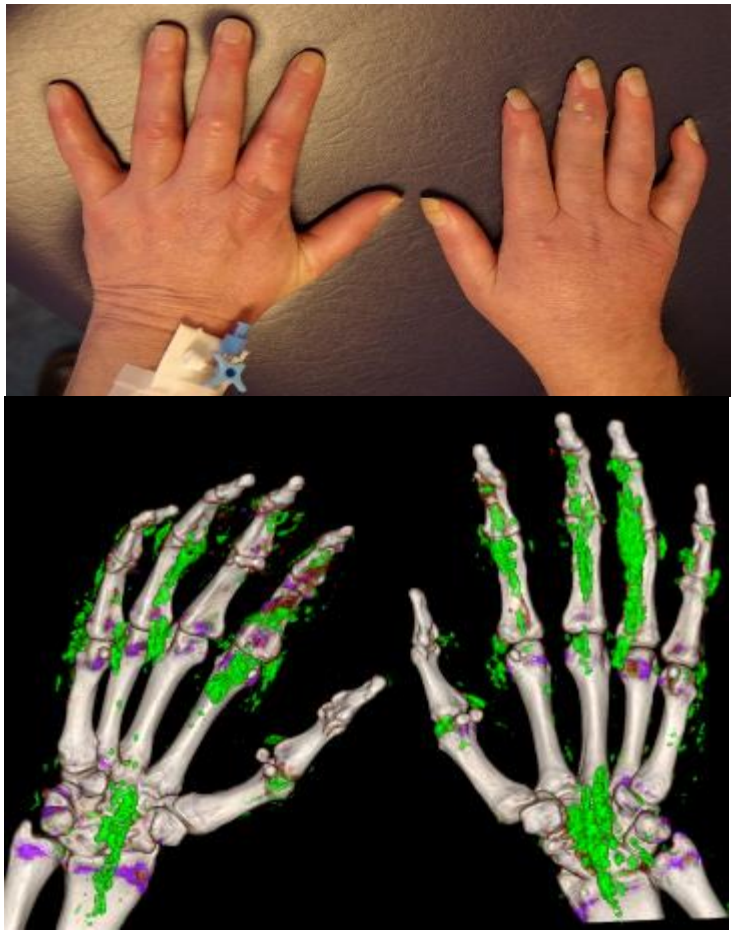
Urate deposition in the body

Small intestine
Mimicking a tumor





Urate burden extends beyond visible tophi

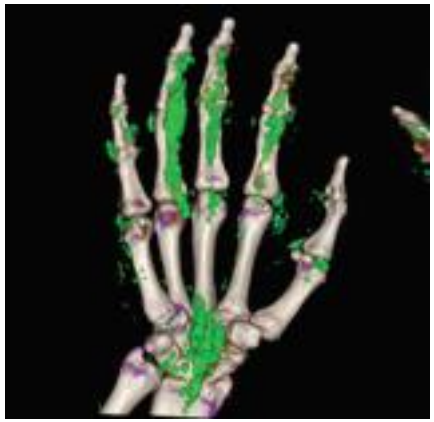


Deposition of MSU crystals detected using DECT (displayed in green). Images courtesy of Dr. Jürgen Rech. Individual patient presentations may vary.

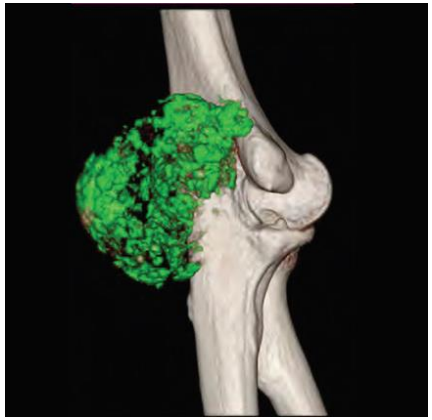
- In addition to visible tophi, MSU crystals can accumulate anywhere in the body
- In a study of 20 patients with gout, significant differences in urate deposits were detected with dual-energy computed tomography (DECT) versus physical examination
  - Only 25% of tophi were detected on physical exam versus DECT

Duel Energy CT (DECT) imaging of urate deposition

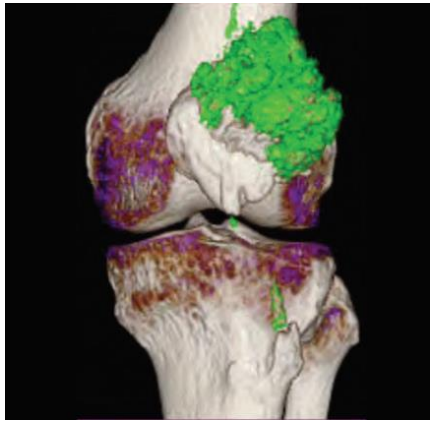
DECT imaging show that a majority of gout patients have non-visible tophi



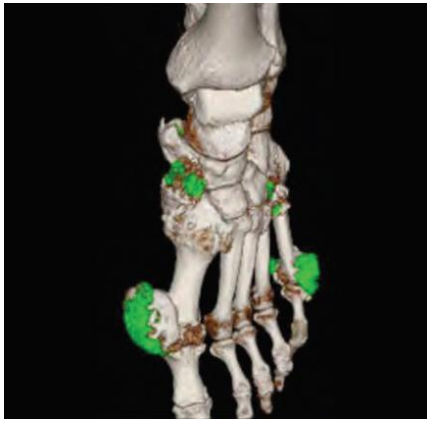
Hands



Elbows



Knees



Feet

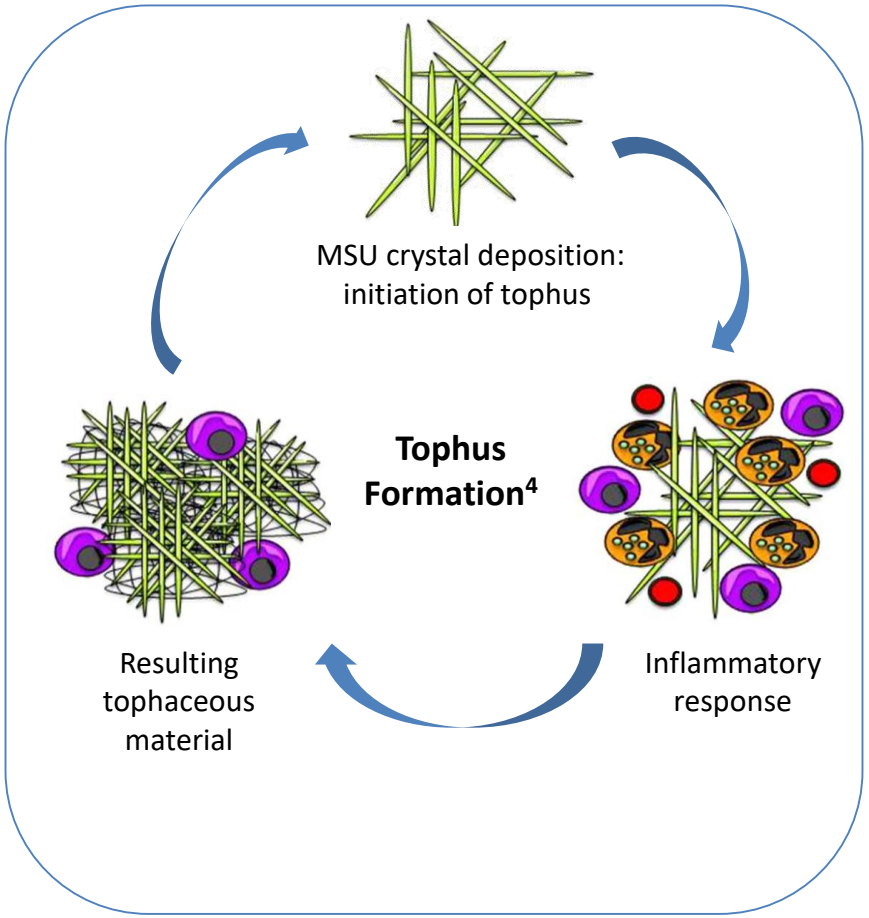
In a DECT study of 40 patients with non-tophaceous gout, 95% had urate deposits present

Bongartz T, et al. *Ann Rheum Dis.* 2014;74:1072-1077.

All gout is technically tophaceous

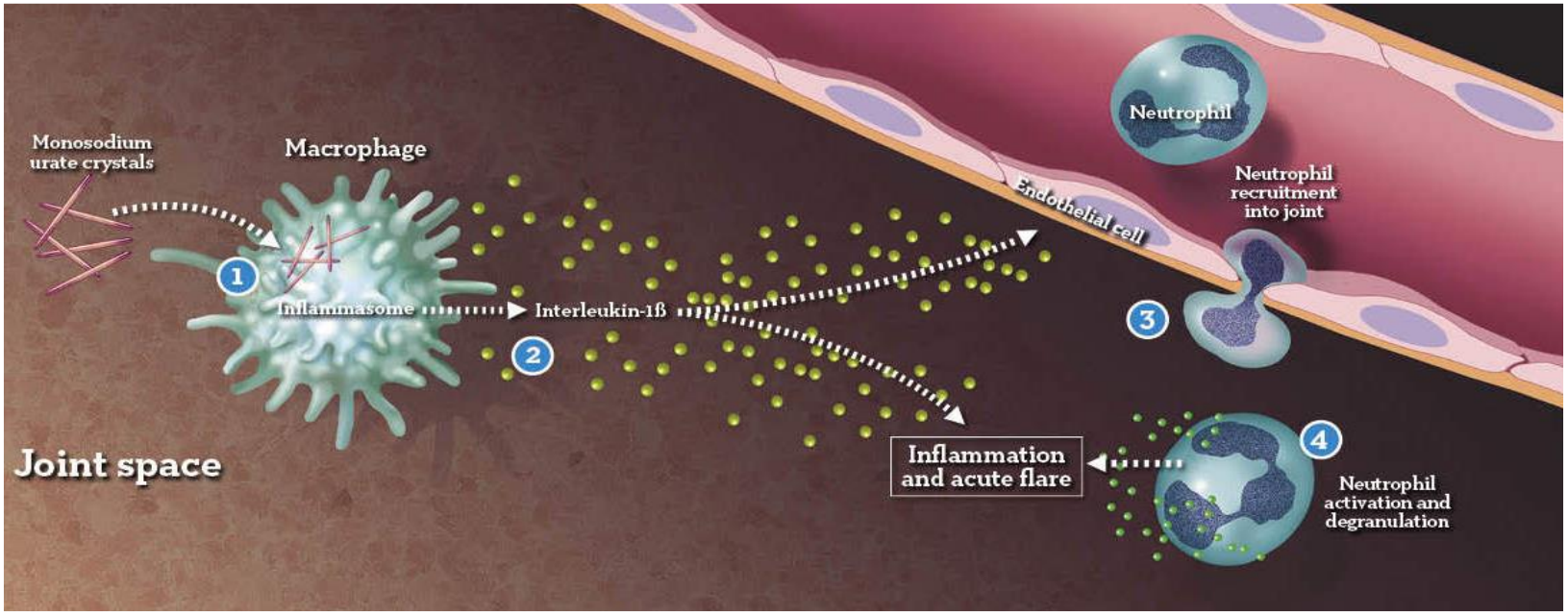
- Systemically, urate crystal deposition initiates the formation of a tophus[4]
- Gout patients are tophaceous by the time the first attack occurs
- Tophi start as small monosodium urate (MSU) aggregates that can only be visualized microscopically

Tophi formation can occur throughout the body, including in organs[3,4,6]



Schett G, et al. *RMD Open*. 2015;1:e000046.11

Crystal-induced systemic inflammation



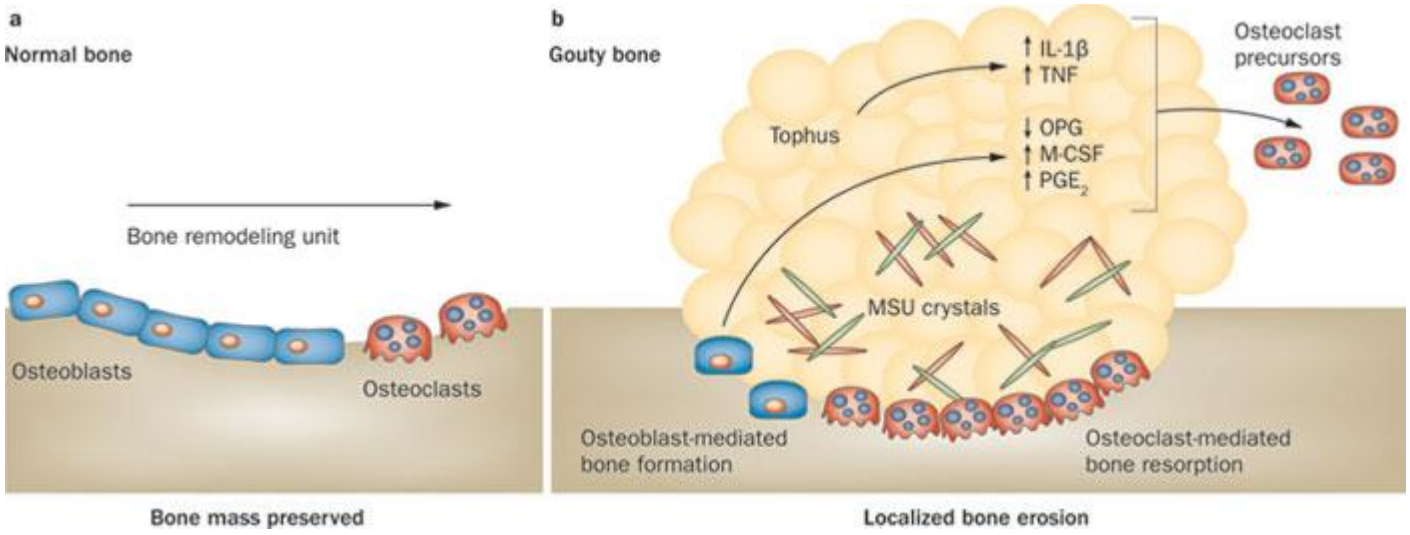
1. Macrophage takes in MSU crystals by phagocytosis

2. Activation of NALP3 Inflammasome triggers IL-1ß

3. Release of IL-1ß triggers neutrophil recruitment and extravasation into the joint space

4. Neutrophil activation leads to the release of proinflammatory compounds

Tophi induces chronic inflammation that can cause bone erosion



- Urate crystal build-up can lead to inflammation and potential destruction of surrounding tissue
- Deposition of urate crystals can lead to destructive skeletal changes

McQueen, F.□M. et□al. Nat. Rev. Rheumatol. 8, 173–181 (2012); published online 10 January 2012; doi:10.1038/nrrheum.2011.207

Consequences of untreated or refractory disease

Treated for osteoarthritis

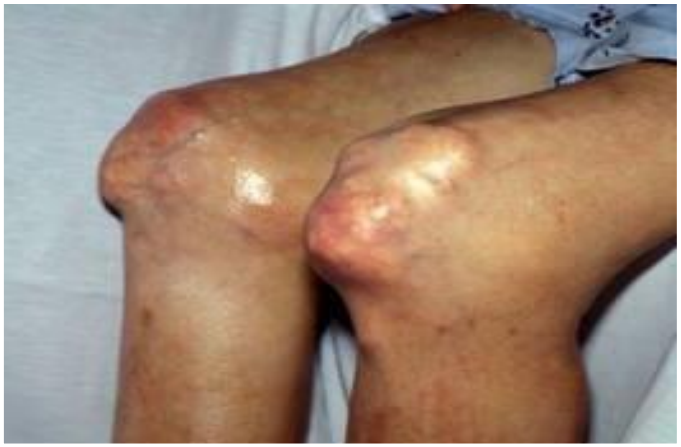


Photo courtesy of Dr. Brian Mandell, Cleveland Clinic

Treated for rheumatoid arthritis

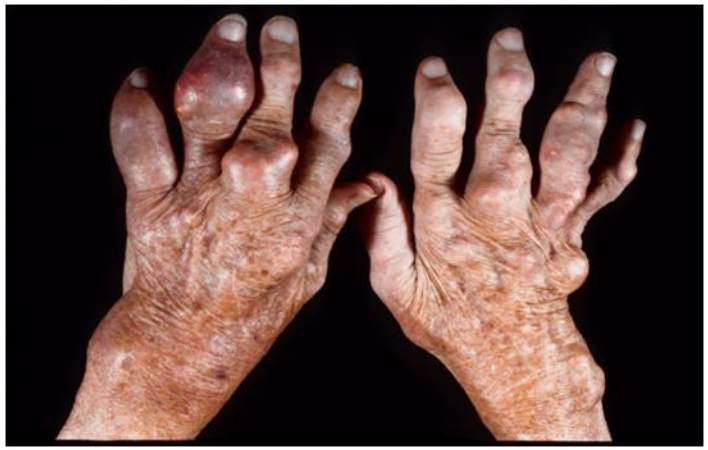
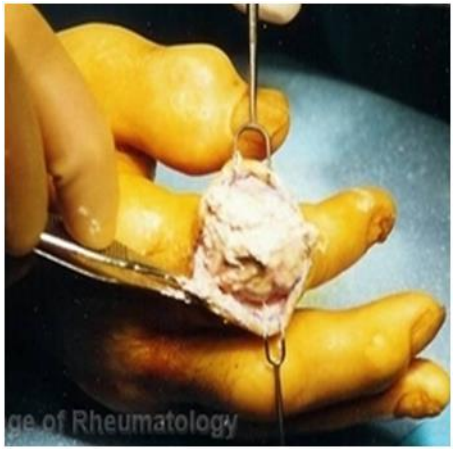
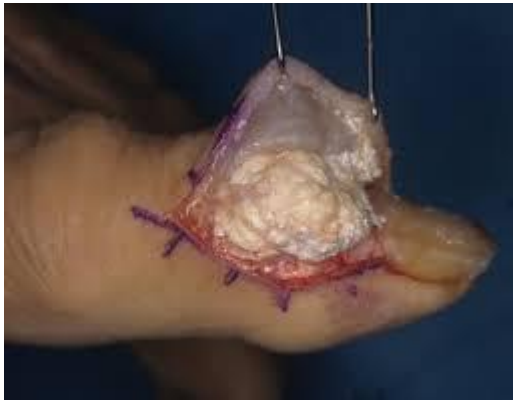


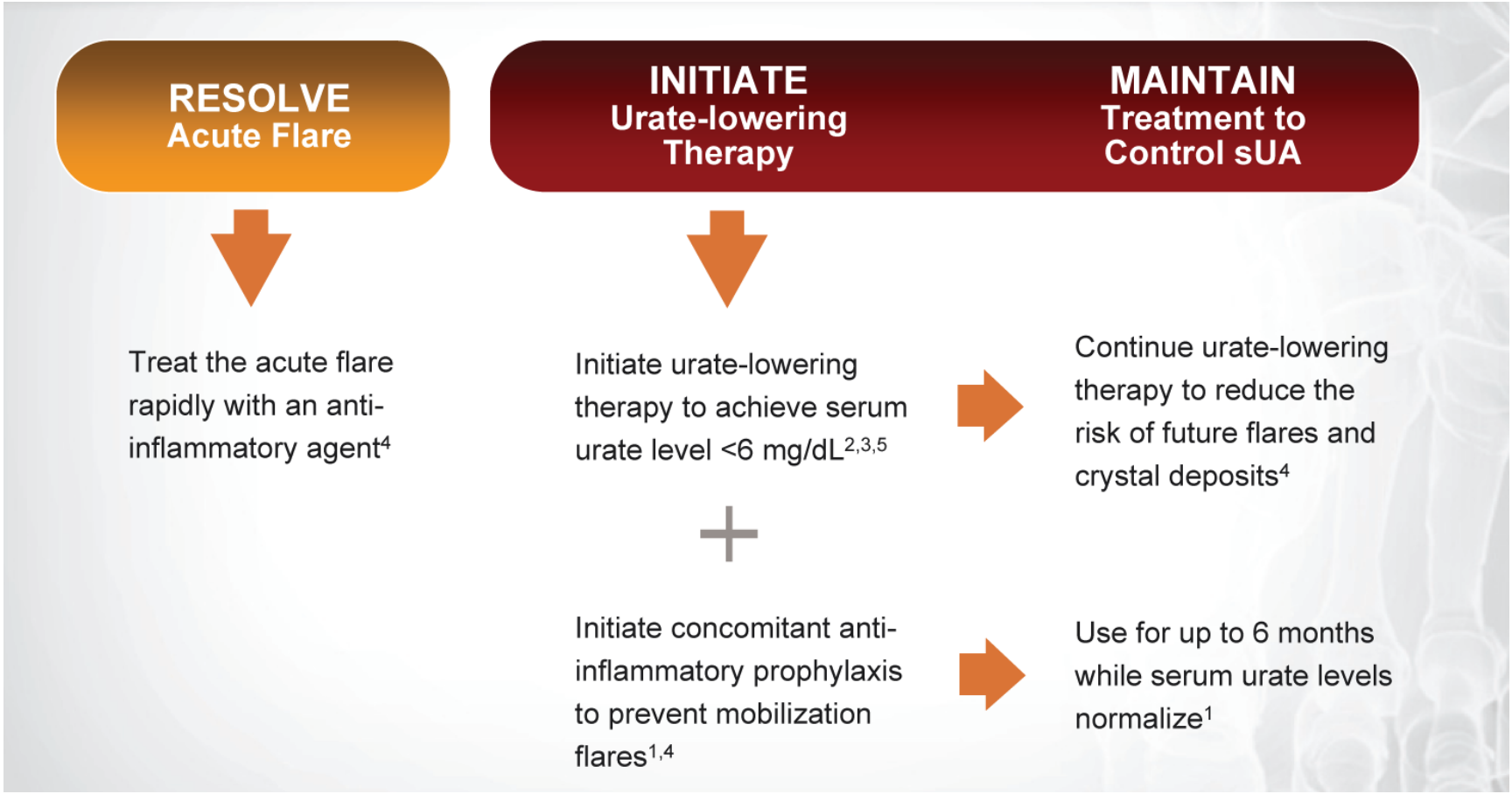
Photo courtesy of Dr. N Lawrence Edwards, Univ. of Florida



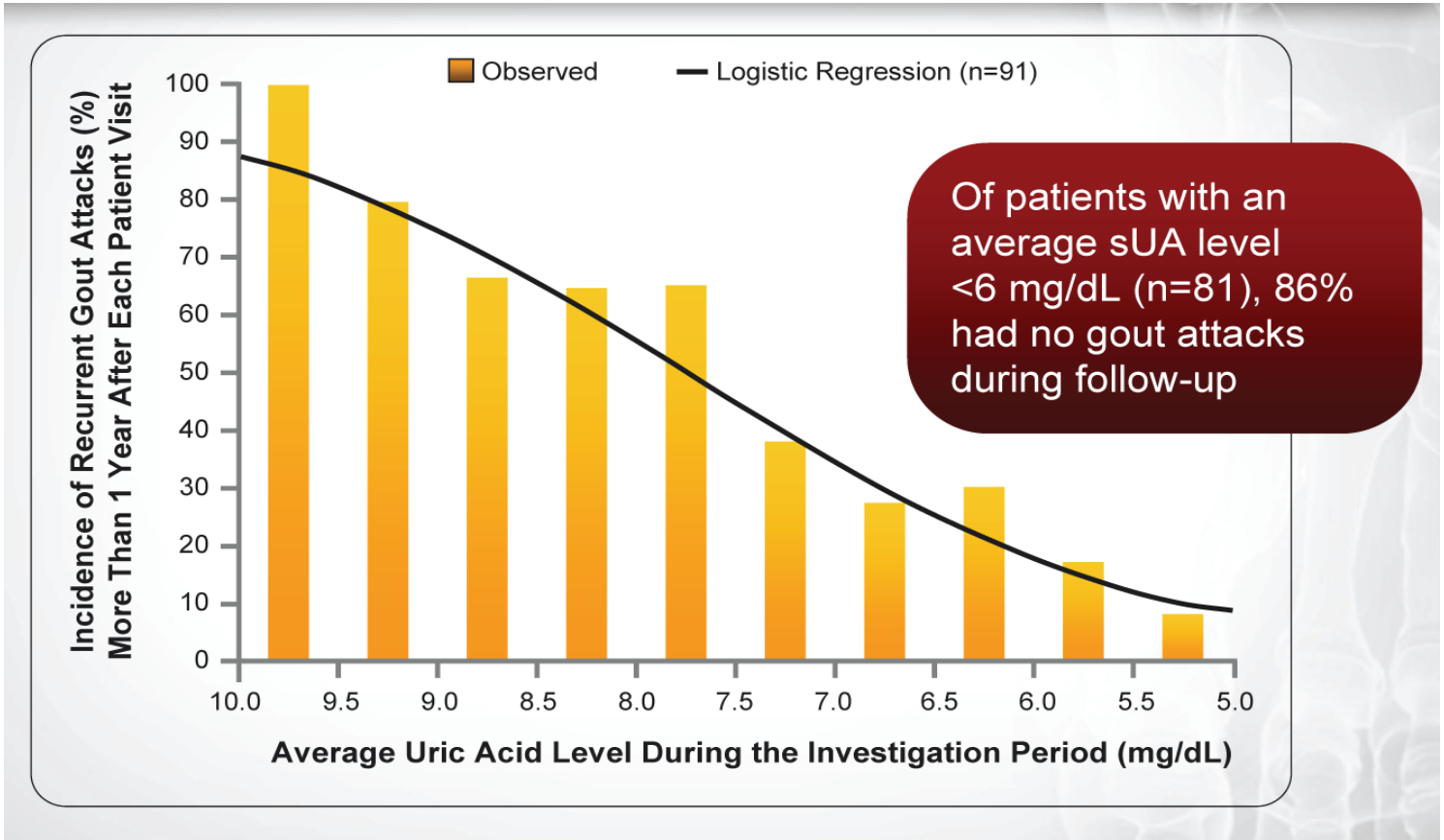


- Invasive surgical intervention
  - Risks and drawbacks
    - High complication rates
    - Delayed wound healing
    - Sepsis/necrosis
    - Potential for worsening
  - Last resort

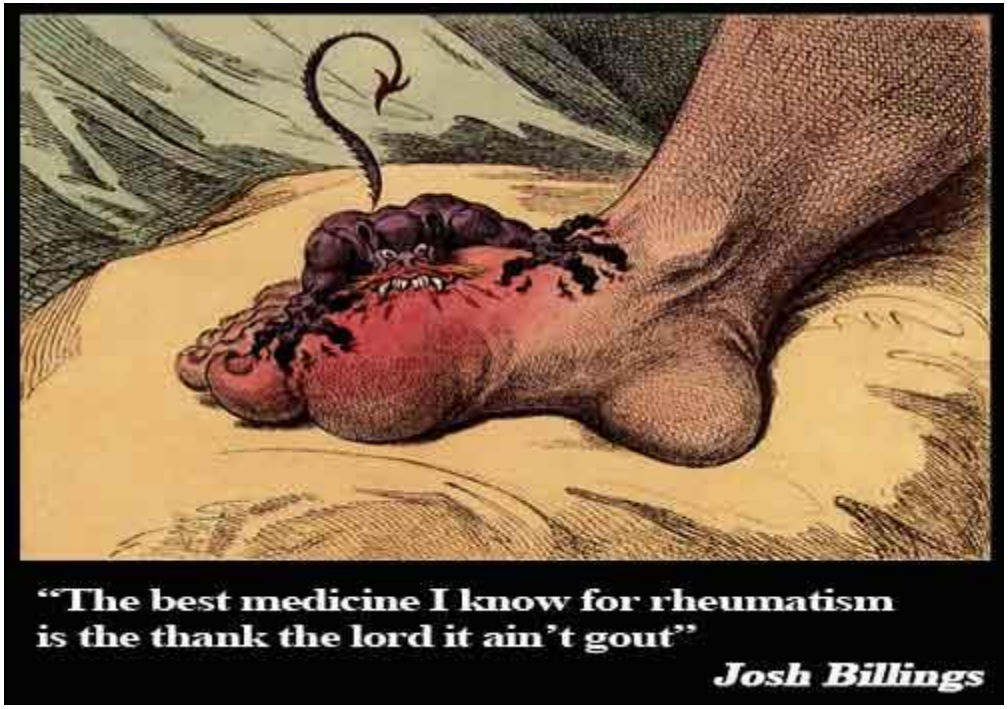
Gout management approach



Maintaining SUA <6 mg/dL is associated with reduced risk of recurrent gout flares

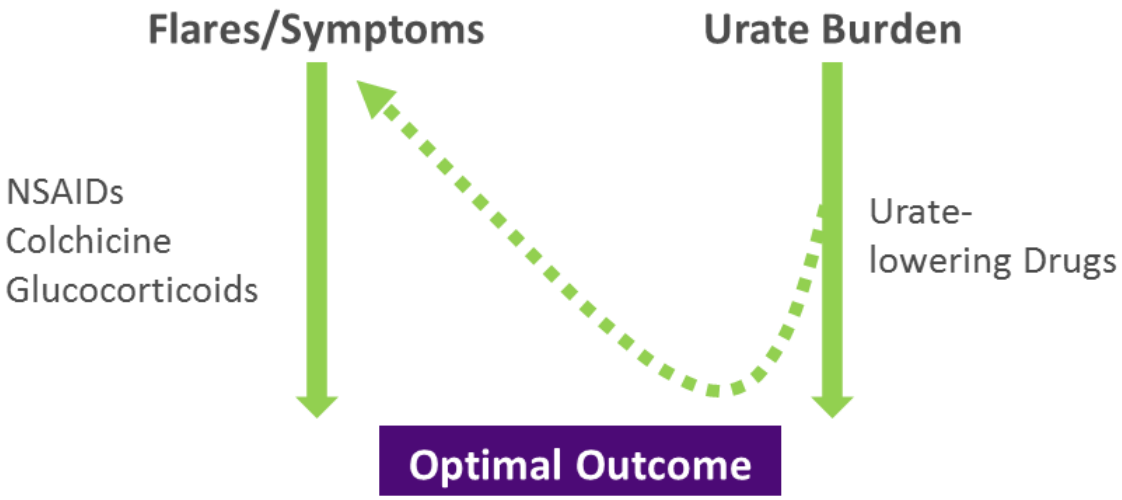


Treatment of gout



Appropriate Management of Gout Requires Control of Both Symptoms and Urate Burden

- In order to achieve optimal patient outcomes, it is important to address 2 processes simultaneously
  - Controlling flares and symptoms
  - Reducing the excess body burden of urate



Adequate treatment of excess urate burden may lead to improvement in clinical manifestations[32]

Classes of urate-lowering therapies

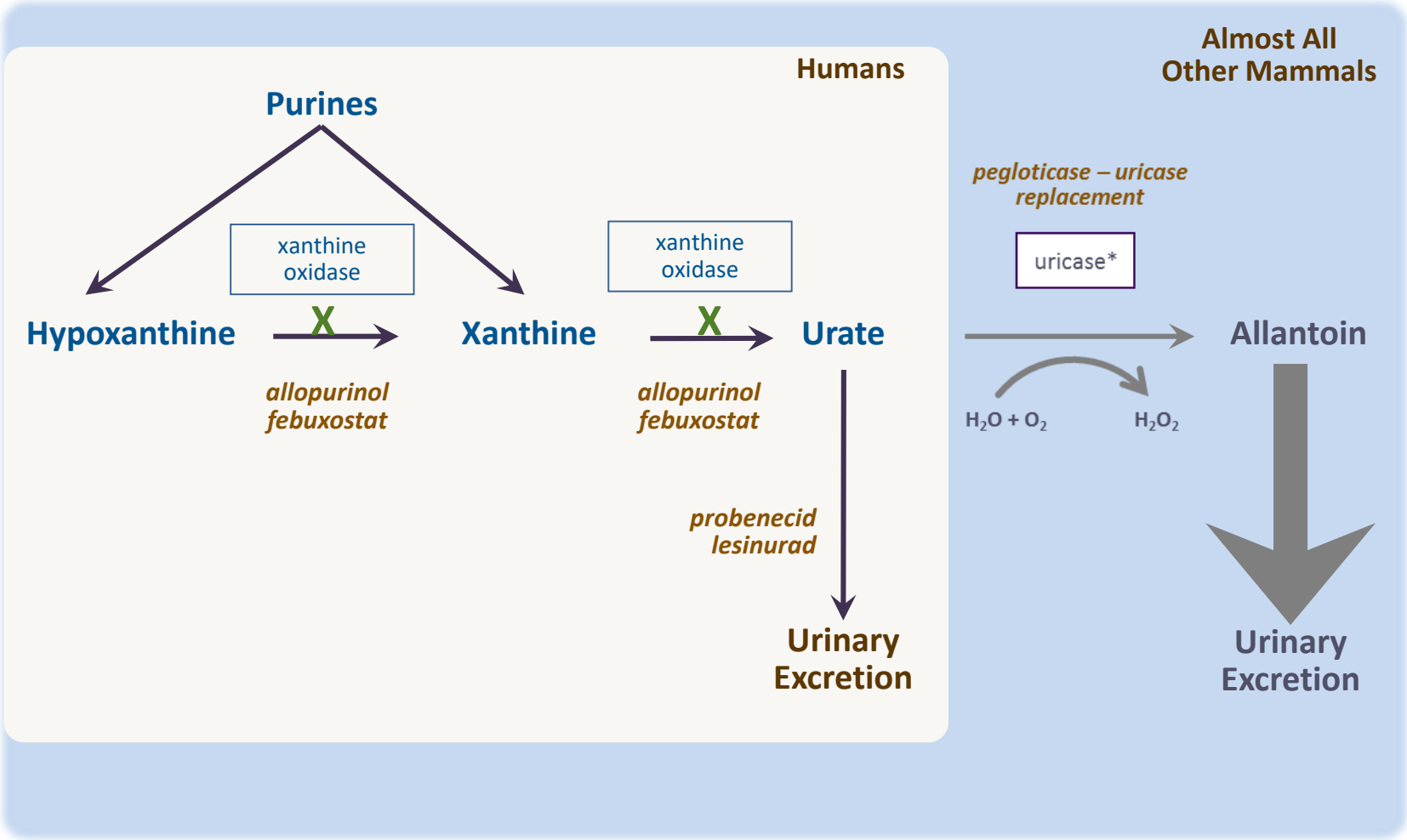
Small molecules

- xanthine oxidase inhibitors
  1. allopurinol
  2. febuxostat
- uricosurics
  1. probenecid
  2. lesinurad

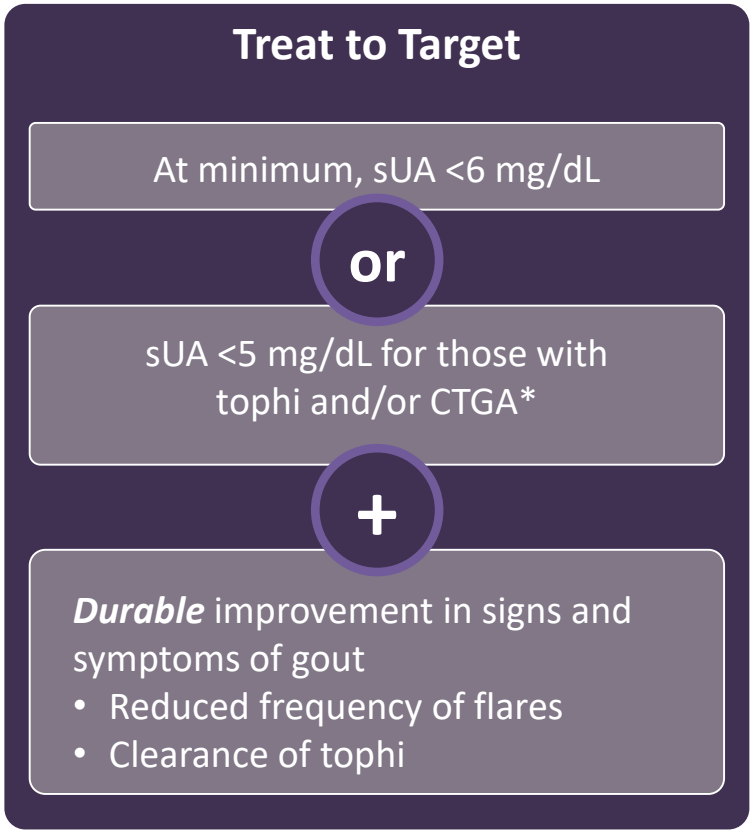
Biologic

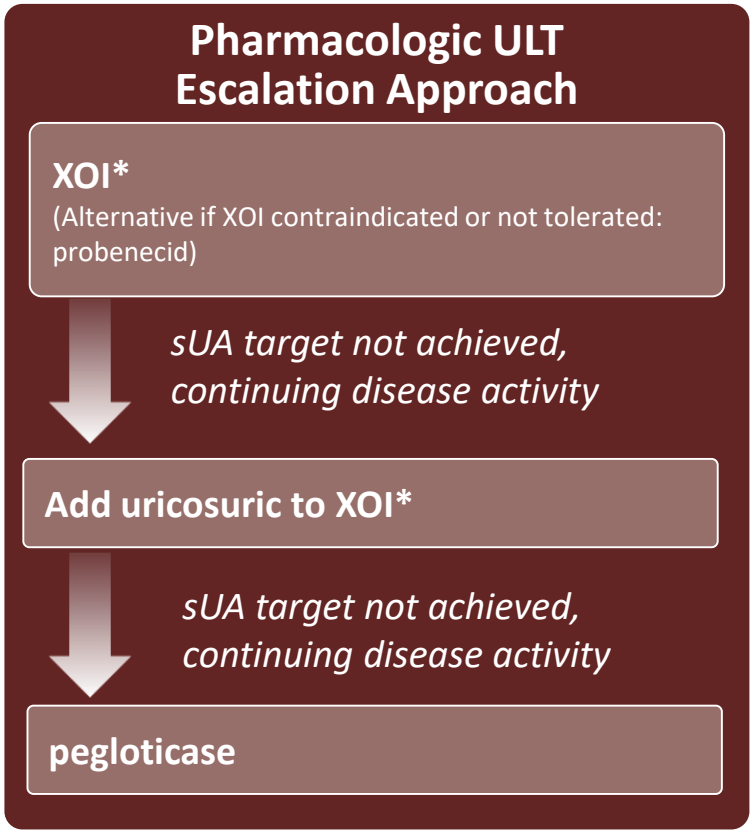
- pegloticase

Purine catabolism



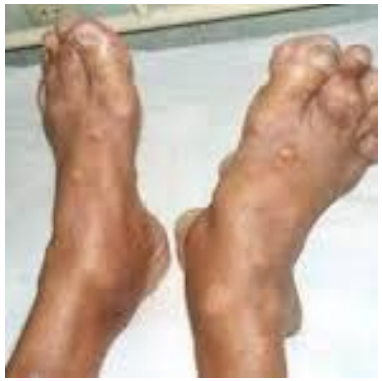
2012 ACR Gout Treatment Guidelines

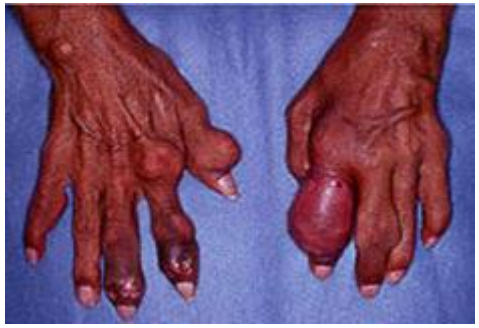




* Titrated to maximum appropriate dose

Management of refractory gout





Definition of refractory gout

- Symptomatic gout in which conventional urate-lowering therapies are contraindicated or the maximum medically appropriate dosage of these therapies does not control hyperuricemia
  - Recurrent and disabling gout flares
  - Chronic gout arthropathy with or without bony erosions
  - Visible progressive tophi
  - Progressive physical disability
  - Poor health-related quality of life

The combination of severe gout, high burden of comorbidities, and polypharmacy can make refractory gout challenging to manage

Patients With Refractory Gout Fail to Achieve Target SUA Levels With Oral ULTs

- Becker, MA, et al. *N Engl J Med.* 2005;353:2450-2461:
  - 79% of patients (n=251) on 300 mg allopurinol/day did not meet target sUA <6.0 mg/dL
  - 47% of patients (n=255) on 80 mg febuxostat/day for 52 weeks did not meet target sUA<6.0 mg/dL

- In about 200,000 gout patients, conventional oral urate-lowering agents fail to achieve target uric acid levels

  Sundy JS, et al. *JAMA*. 2011;306(7):711-720

Treatment options for Refractory Gout

- Dose escalation of conventional urate lowering therapies:
  - allopurinol to 800 mg daily in divided doses
  - febuxostat to 160 – 240 mg daily
  - probenecid to 1000 mg daily in divided doses
  - lesinurad to 200 mg daily
- Combination therapy: xanthine oxidase inhibitor + uricosuric
- Lifestyle modifications
  - diet
  - exercise
  - cherry extract
  - vitamin C
  - losartan for diuretics
  - fenofibrate for niacin
  - avoidance of high fructose corn syrup
  - low fat dairy products
- Biologic therapy
  - pegloticase

Pegloticase: a biologic approved for the treatment of refractory gout

- pegloticase is a uric acid-specific enzyme, which is a PEGylated product that consists of recombinant modified mammalian urate oxidase (uricase)
- pegloticase achieves its therapeutic effect by catalyzing the breakdown of uric acid to allantoin
  - allantoin is more water soluble than uric acid and is readily excreted by the kidneys, leading to lowering of sUA levels
- the long-term safety & efficacy profile of pegloticase has been studied in patients receiving treatment for up to 3 years

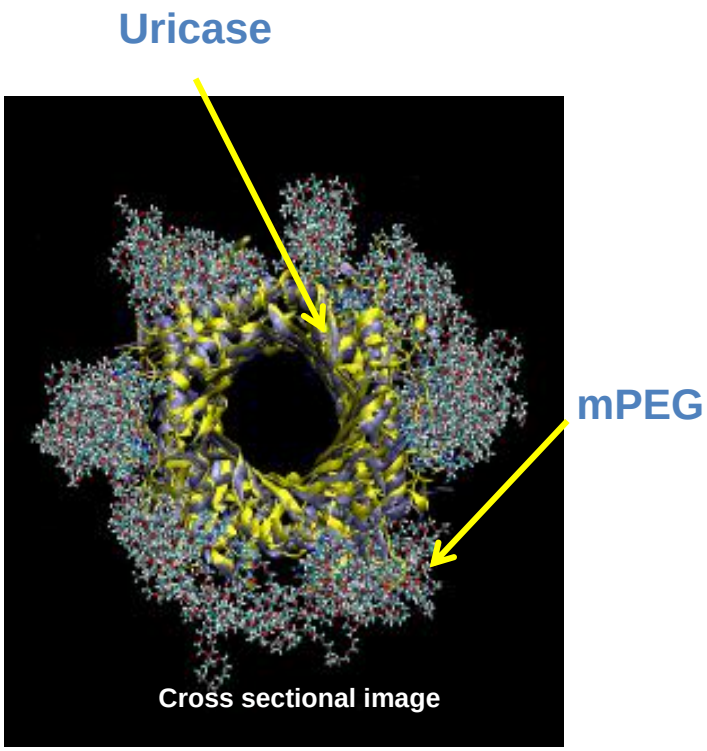
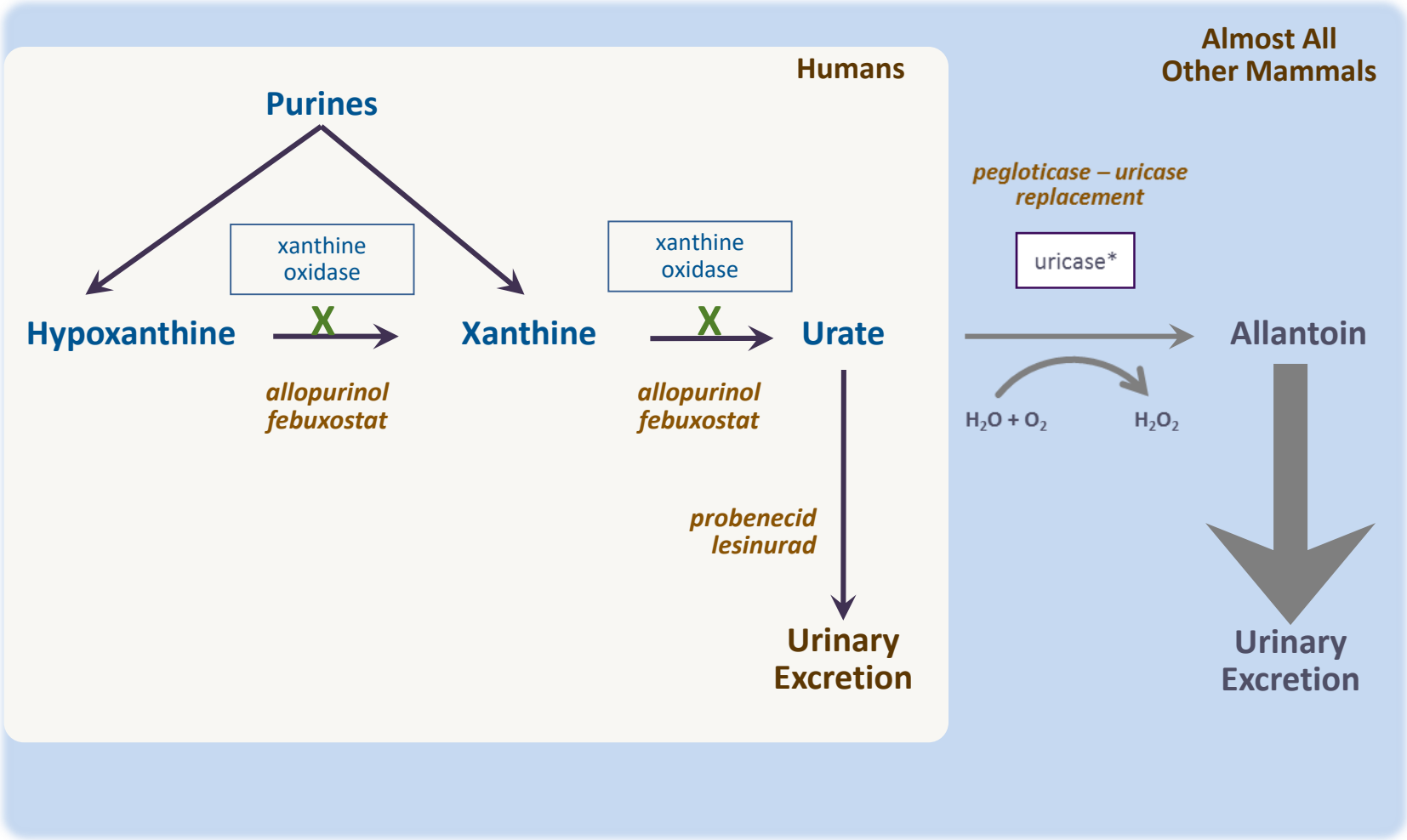


Figure courtesy of Toby Sannan and Christopher Hadad, Ohio State University.

Purine catabolism



Phase III trials - pegloticase

- Two replicate, multicenter, randomized, double-blind, placebo-controlled trials of 6 months duration
  - Subjects included adults with chronic gout refractory to conventional therapy
  - 8 mg pegloticase infusions were studied in two dose regimens (q2wks and q4wks) versus placebo

PRIMARY ENDPOINT

- Percentage of plasma uric acid (PUA) responders versus placebo
- **Complete Responders**
  - Patients who achieved PUA concentration <6 mg/dL for at least 80% of the time during both months 3 and 6
- **Incomplete Responders**
  - Patients who did not sustain uric acid levels <6 mg/dL throughout the trial
  - Patients who withdrew before the final visit

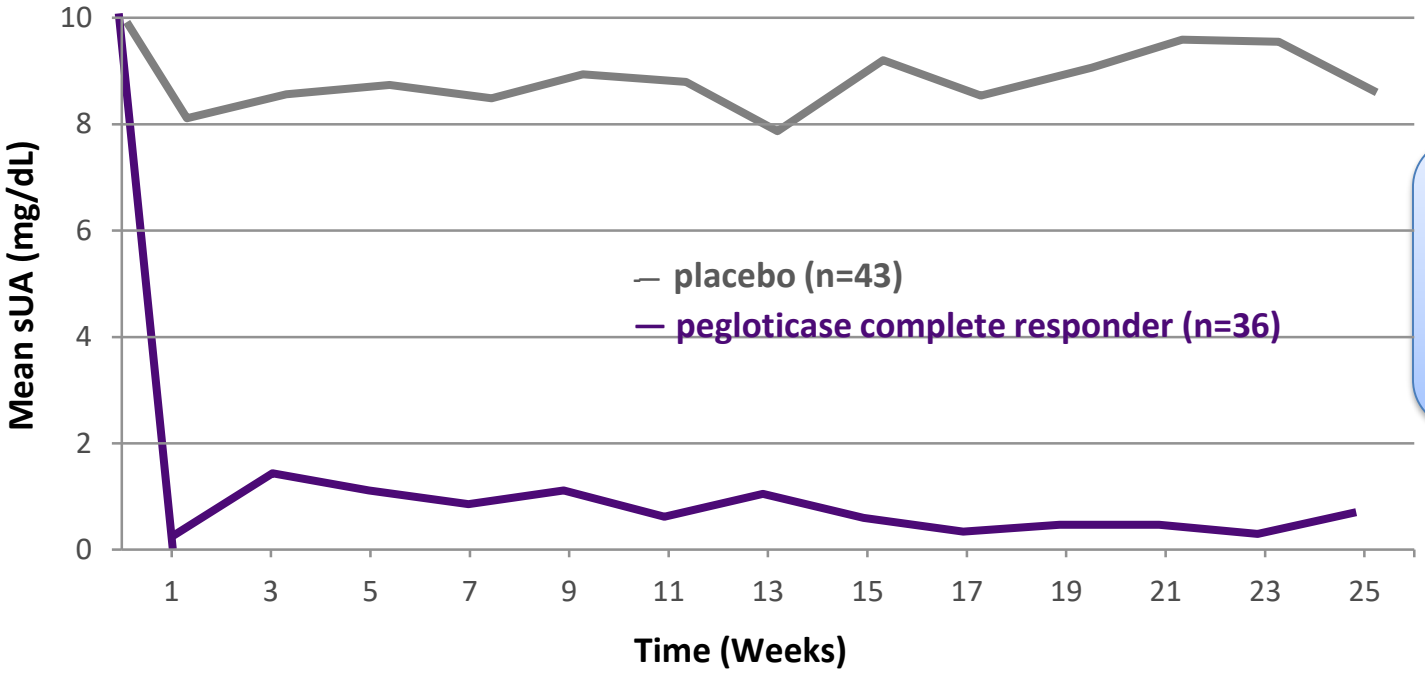
SECONDARY ENDPOINT

- **Complete resolution (CR) of tophi**
  - Defined as 100% resolution of at least 1 target tophus, with no new or progressive tophi

Phase III trials – Baseline characteristics

- Patient characteristics
  - Mean age: 55 (23-89)
  - Predominantly male (82%)
  - Mean BMI: 33 kg/m
- Patient disease characteristics
  - Mean disease duration: 15 years
  - Mean baseline sUA: 10 mg/dL
  - Mean flares: 10 in prior 18 months (7 in past year)
    - 63% described flares as severe/crippling
  - 71% with visible tophi

Pooled Pivotal Trials Results: Complete Responders

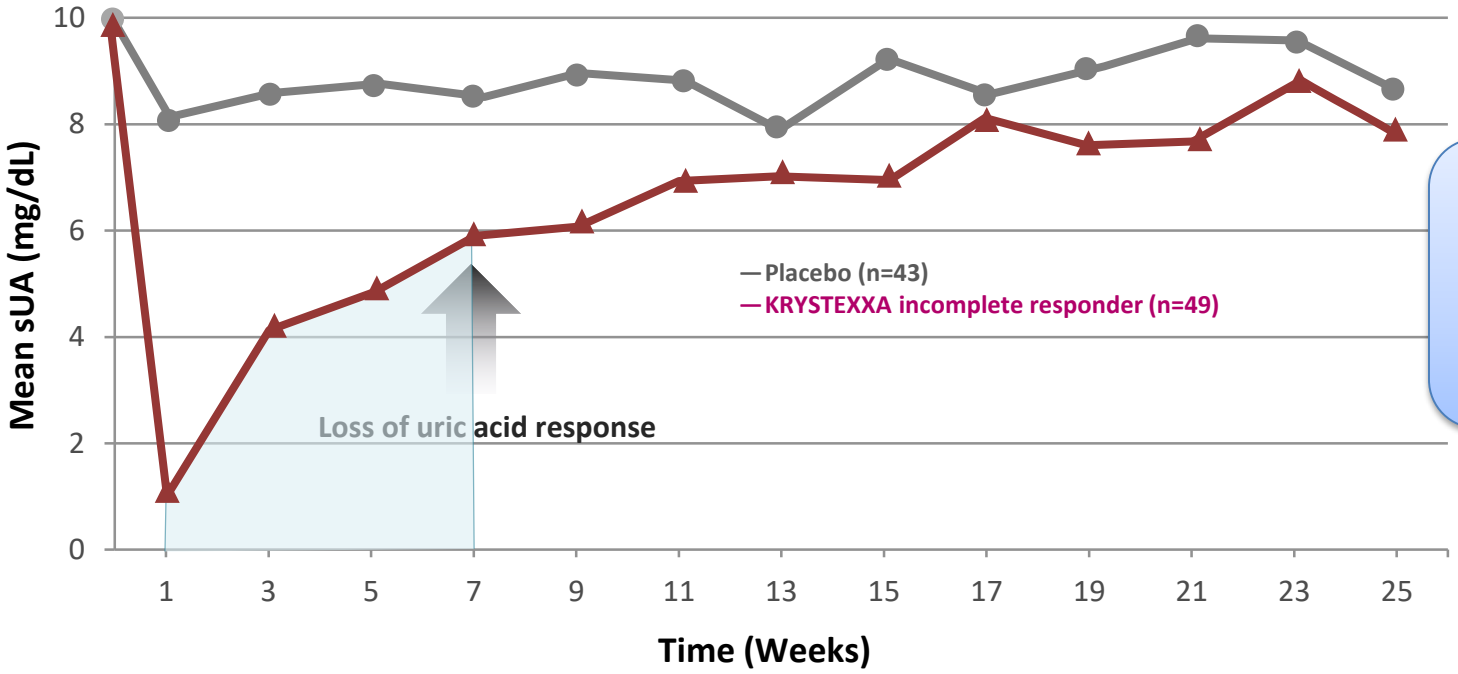


42%

of patients had a complete response

- These patients maintained sUA levels below 6 mg/dL 80% of the time at months 3 and 6 versus 0% for placebo ($P<0.001$)

Pooled Pivotal Trials Results: Incomplete Responders



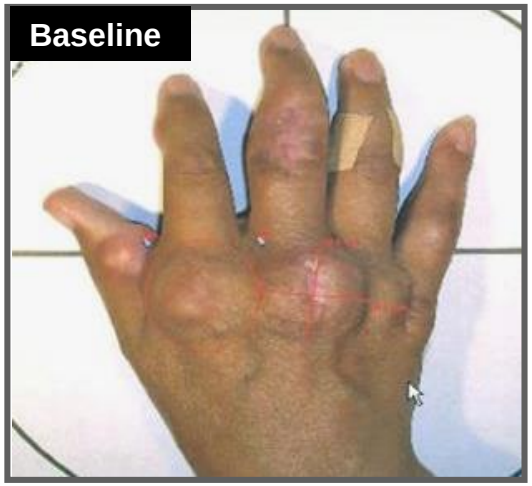
58%

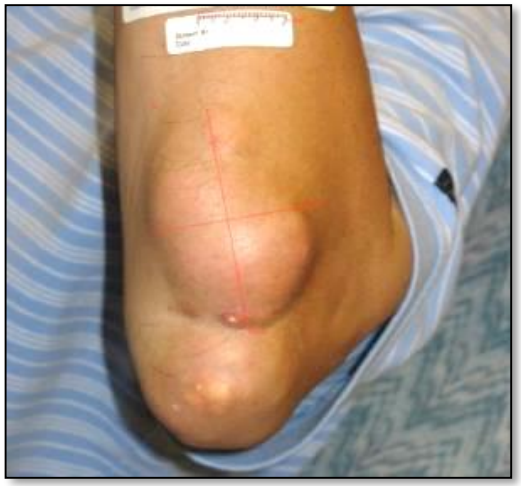
of patients had an incomplete response

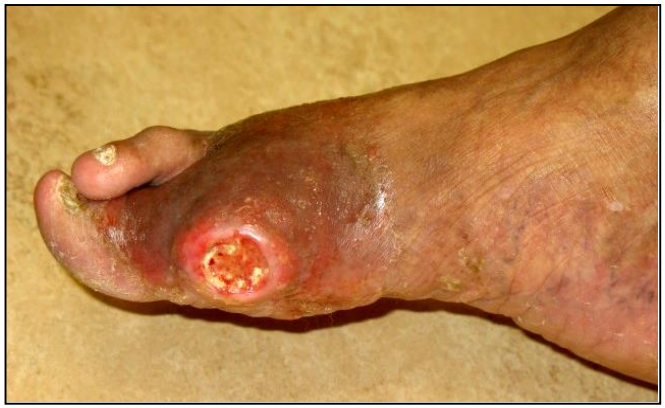
- These patients achieved a significant reduction in sUA for a mean of 7 weeks, allowing some clearance of the urate burden ($P<0.001$). The response was not durable; therefore, they did not meet the primary endpoint.

Secondary endpoint – Tophus resolution

- 71% of patients had 1 or more tophi at the baseline of the study







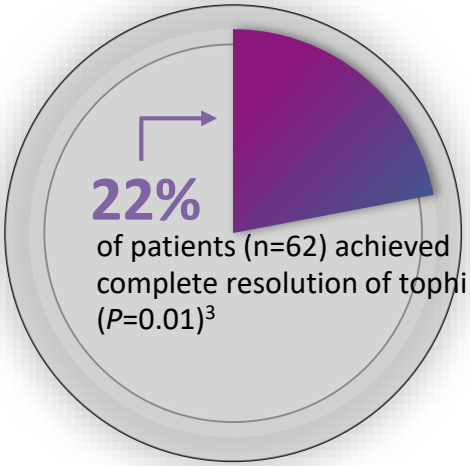
Secondary endpoint – Tophus resolution

SECONDARY ENDPOINT[1,2]

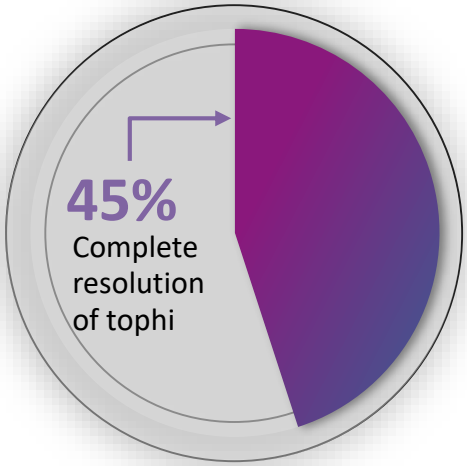
Complete resolution of tophi

Defined as 100% resolution of at least 1 target tophus, with no new or progressive tophi

At 3 Months



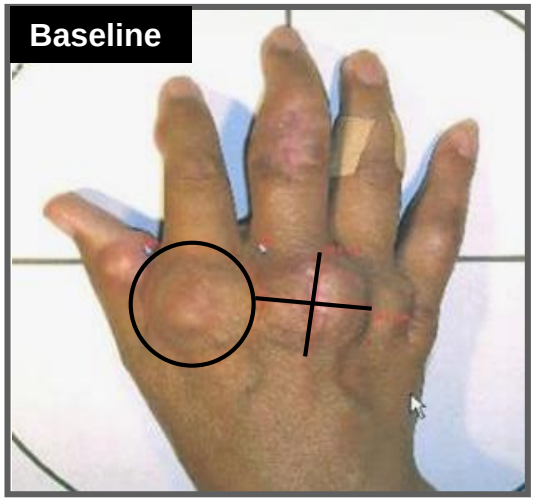
At 6 Months



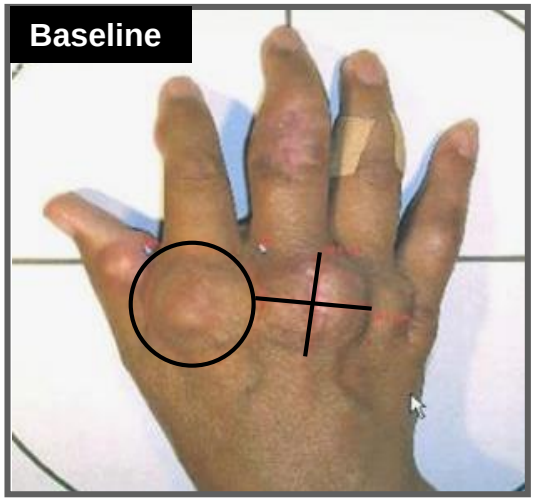
These results include patients who experienced a complete response as well as patients who experienced an incomplete response in the primary endpoint[3]

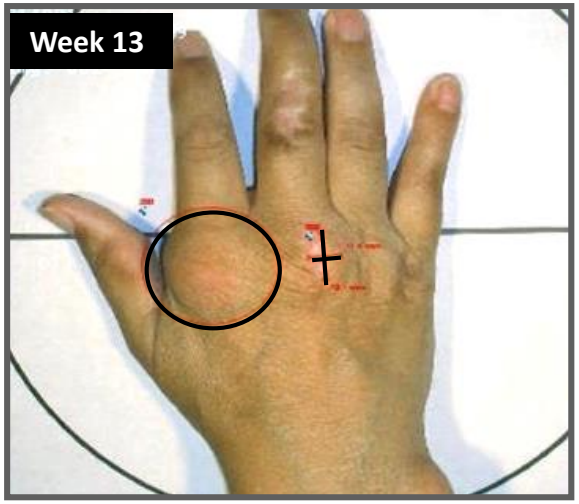
- 45% (18/40) of patients treated with pegloticase (q2wk) achieved a complete resolution of their target tophus versus 8% (2/25) of patients receiving placebo (*P*=0.002)

Secondary endpoint – Tophus resolution

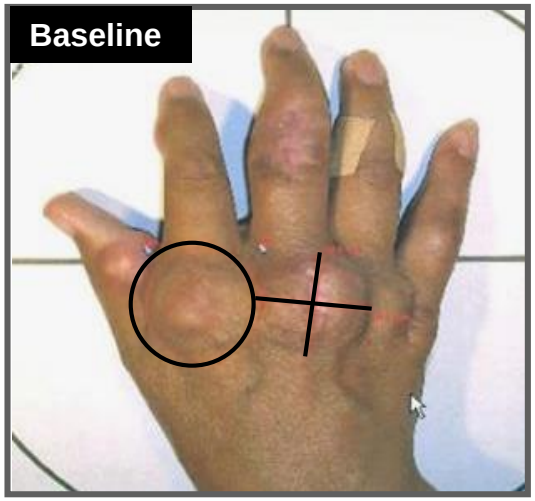


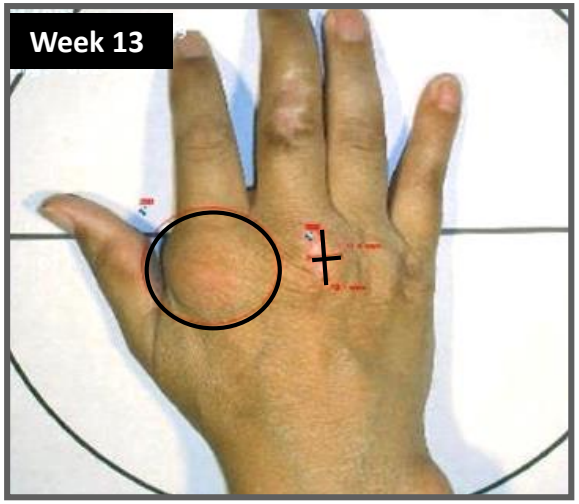
Secondary endpoint – Tophus resolution

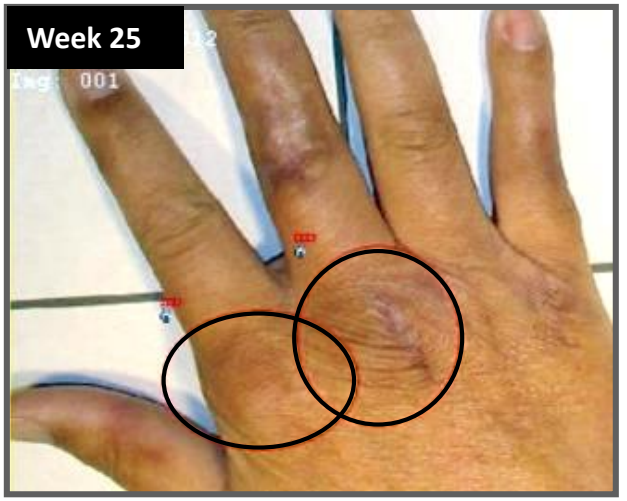




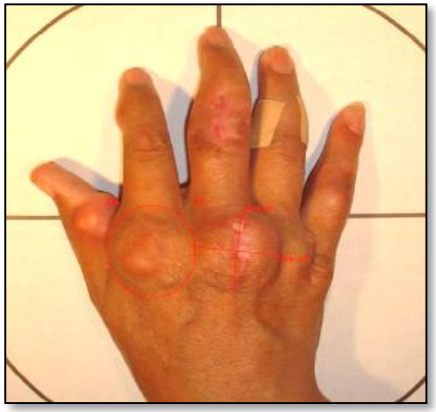
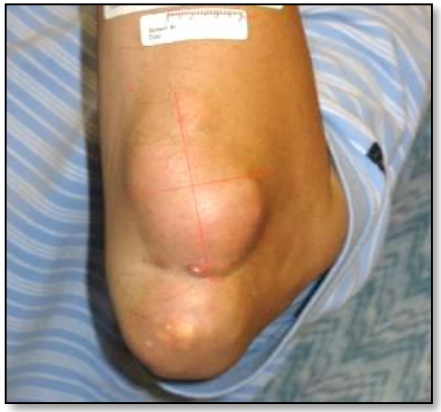
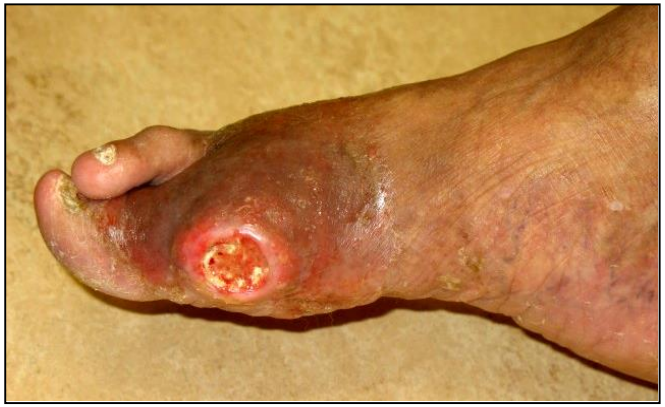
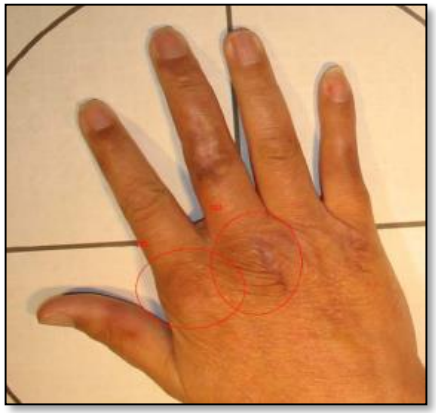
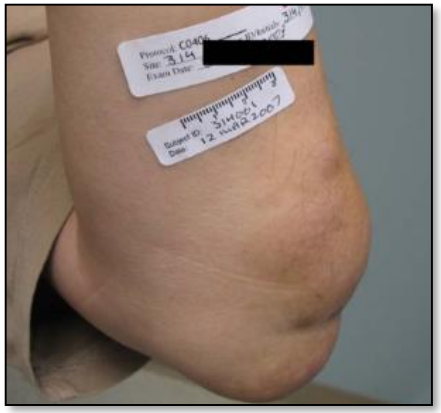
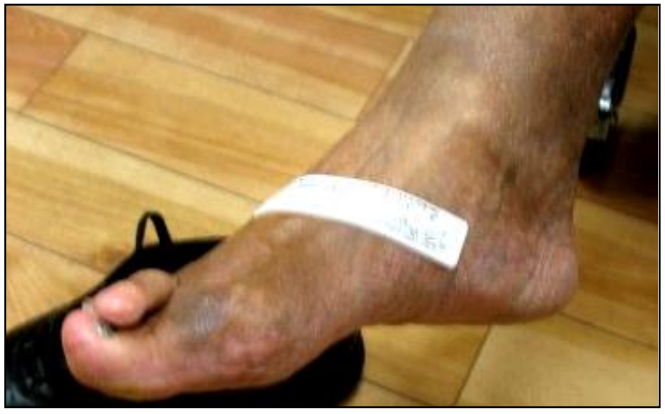
Secondary endpoint – Tophus resolution





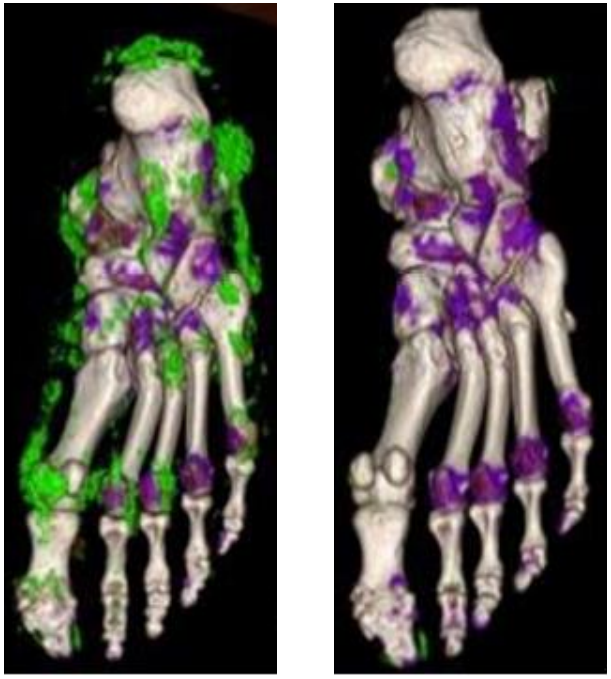


Secondary endpoint – Tophus resolution

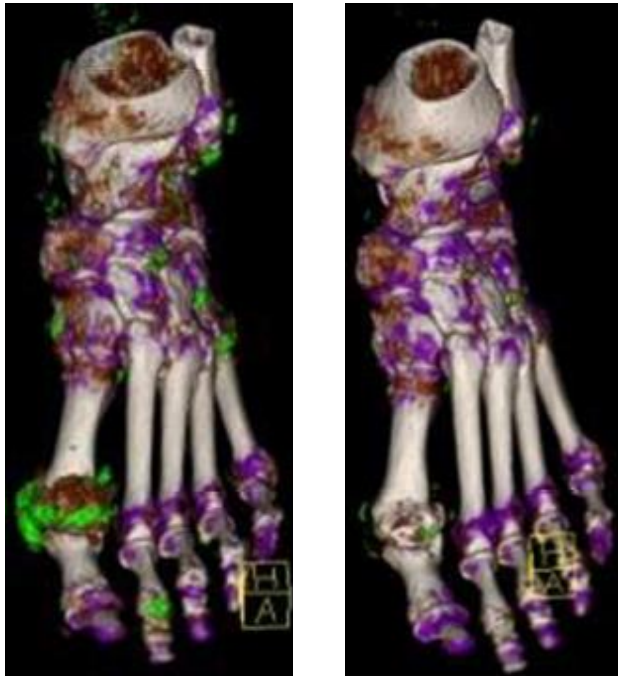
DECT imaging: Resolution of tophi after pegloticase

DECT Imaging of Tophi (Green) in a Responder



Before Treatment | After Treatment

DECT Imaging of Tophi (Green) in a Partial Responder



Before Treatment | After Treatment

Safety: Adverse events

Most Common Serious Adverse Reactions Occurring in at Least 5% of Patients Treated With pegloticase		
Adverse Reaction (Preferred Term)	**Pegloticase 8 mg q2wk (N=85) n[a] (%)**	**Placebo (N=43) n (%)**
Gout flare	65 (77)	35 (81)
Infusion reaction	22 (26)	2 (5)
Severe infusion reaction*	4 (5)	0 (0)

- Other most common adverse reactions occurring in at least 5% of patients treated with pegloticase: nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, and vomiting

Safety: Adverse events

- Most infusion reactions (IRs) occur when sUA levels are >6 mg/dL
- If sUA levels increase to >6 mg/dL on therapy, patient is likely to have anti-pegloticase antibodies, hence an increased risk of infusion reactions
- If sUA is monitored closely and subjects do not receive pegloticase after the sUA has returned to >6 mg/dL, most IRs could be avoided

	Pegloticase 8 mg q2wks N = 22
sUA >6 mg/dL before infusion reaction	20/22 (91%)
sUA <6 mg/dL	1/22 (4.5%)
Infusion reaction at first dose*	1/22 (4.5%)

Safety: Infusion reactions (IRs) and anaphylaxis

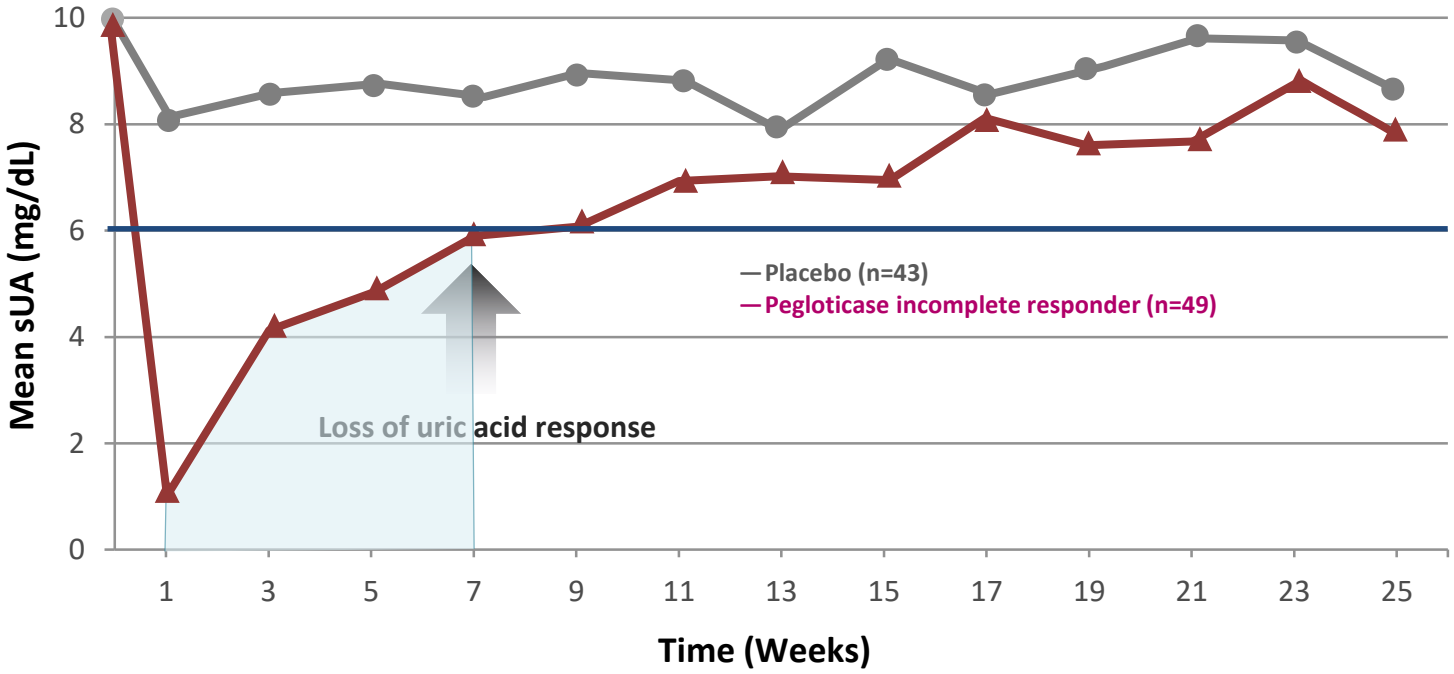
- During the pivotal clinical trials, IRs were segmented by severity—mild, moderate, or severe
- IRs occurred in 26% (22/85) subjects treated with pegloticase 8 mg every 2 weeks compared to 5% (2/43) of subjects treated with placebo
- There were 4 cases (5%) of severe IRs identified by physicians that were retrospectively reclassified as anaphylaxis by the FDA*
- Of the 4 cases reclassified as anaphylaxis, 3 likely would have been prevented using the pegloticase sUA stopping rules

* Diagnostic criteria (post-hoc FDA analysis using NIAID/FAAN criteria):
  - Skin or mucosal tissue involvement, and either airway compromise and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to pegloticase or placebo injection with no other identifiable cause

Safety:

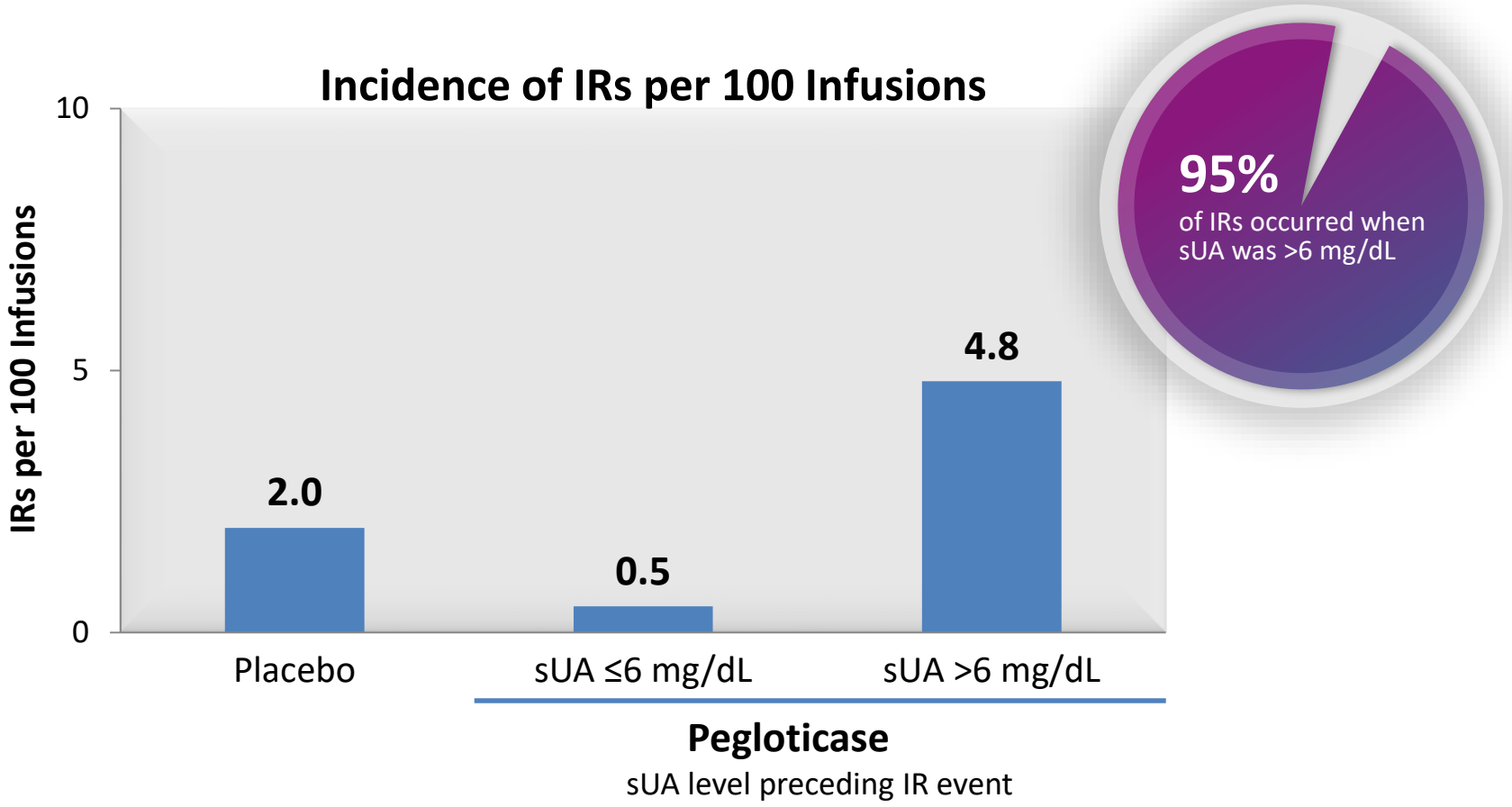
- No patients with IRs required intubation, mechanical ventilator support, vasopressors, or hospitalization.
- There were no infusion-related deaths.

Safety: Post-hoc analysis



Most Infusion Reactions Occurred When sUA >6 mg/dL

Pre-infusion sUA Levels Are a Powerful Marker for Predicting IRs



Using SUA as a predictive biomarker

Stopping rule:

- Check a SUA 48 hours before the next pegloticase infusion:
  - If SUA <6 mg/dL, infusion can be given
  - If SUA >6 mg/dL, consider discontinuing treatment, particularly when 2 consecutive sUA levels >6 mg/dL are observed

If this stopping rule is utilized, the majority of infusion reactions can be avoided

No other biologic in Rheumatology has a predictive biomarker

Safety: Pre-infusion protocol

Infusion Premedication	Gout Flare Prophylaxis	Oral ULT
• Antihistamine the night before and morning of each infusion • Acetaminophen morning of each infusion • Corticosteroid prior to each infusion	• Colchicine, NSAID, or both • Initiated 1 week before first infusion • Recommended for at least the first 6 months of therapy	• Discontinue before starting pegloticase

It is important to measure sUA levels prior to infusion

Collaboration between podiatrists & rheumatologists

- Latest treatment options mark a watershed moment in the management of gout
- Podiatrists role in gout management today is now more critical than ever
  - Increased emphasis on comprehensive, collaborative, and correlated care amongst healthcare providers
  - “First responders” of gout flares
  - Surgical management of refractory tophaceous gout
  - Missing link between a patient’s PCP and rheumatologist

Collaboration between podiatrists & rheumatologists

Lansdowne *et al. Journal of Foot and Ankle Research* (2015) 8:14
DOI 10.1186/s13047-015-0071-z

JOURNAL OF FOOT
AND ANKLE RESEARCH

RESEARCH Open Access

Perceived barriers to the management of foot health in patients with rheumatic conditions

Nina Lansdowne, Angela Brenton-Rule, Matthew Carroll and Keith Rome*

Results

- 56 podiatrists responded to web-based survey
- Results demonstrated poor integration of podiatrists into multidisciplinary teams
- Only 16% reported being part of an established multidisciplinary team
- 95% expressed interest in professional development for the podiatric management of arthritic conditions

Conclusions

- There are barriers in the involvement of podiatrists in the management of people with rheumatic conditions

Overcoming barriers between podiatrists and rheumatologists in the care of gout patients

- Identify a local rheumatologist who has a common interest in gout
- Foster collaborative relationship
  - Direct contact for referrals and timely consultations
  - Dual podiatry-rheumatology clinics
  - Develop co-management strategy
    - Delineation of roles
    - Identification of common ground
  - Joint community outreach

Summary

- Gout is a chronic, progressive arthritis caused by hyperuricemia with associated chronic inflammation
- Body urate burden extends beyond clinically and physically apparent tophi
- Gout can be difficult to treat, beyond management with xanthine oxidase inhibitors and uricosurics
- Pegloticase is the first biologic and only FDA-approved treatment option for patients with chronic refractory gout
- Pegloticase can be an effective option for patients with chronic refractory gout

Thank you