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4:00 – 4:35 pm

New Drugs for the Primary Care Provider: What You Need to Know

SPEAKER
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primed

Presenter Disclosure Information

The following relationships exist related to this presentation:

- Gerald W. Smetana, MD: No financial relationships to disclose.

Off-Label/Investigational Discussion

- In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

New Drugs for the Primary Care Provider: What You Need to Know

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Important New Drugs for 2016: What We Need to Know

Novel Drugs

Relevant for PCP

No "Me Too" Drugs

new and improved

2016:
Fewer New Drug Approvals and Fewer Relevant for Primary Care...

FDA New Drug Approvals in 2016: Slim Pickings for Primary Care

Novel Drugs, 2

Me Too Drugs, 1

Subspecialty Biologics, 5

Subspecialty Meds, 11

Three Novel Drugs for Primary Care Practice

- Mepolizumab for Rx of severe eosinophilic asthma
- Patiromer for hyperkalemia
- Lesinurad to lower uric acid levels in gout

Historical Perspective

"Man has an inborn craving for medicine... The desire to take medicine is one feature which distinguishes man, the animal, from his fellow creatures... Even in minor ailments, which would yield to dieting or to simple home remedies, the doctor's visit is not thought to be complete without the prescription."

William Osler 1895

Mepolizumab for Rx of severe eosinophilic asthma



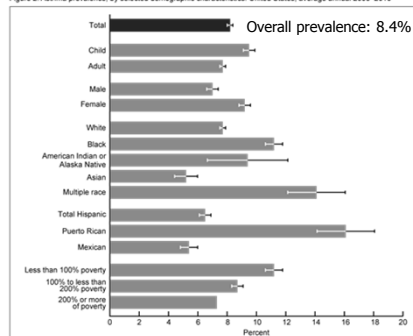
First Available mid-2016

Mr. Al Buterol

- 36 year old man
- Severe, persistent asthma
- 3 admissions in past year
- Unable to drop below prednisone 10 mg qd
- Is this new Rx for me?

Asthma Prevalence in the U.S. 2010

Figure 2. Asthma prevalence, by selected demographic characteristics: United States, average annual 2008–2010

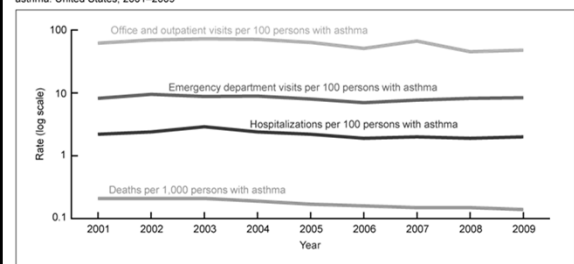


NOTE: Asthma prevalence refers to percentage of people who have ever been diagnosed with asthma and still have asthma. Access data table for Figure 2 at http://www.cdc.gov/nchs/data/asthma/asthma_prevalence_2008-2010.pdf.
SOURCES: CDC/NCHS, Health Data Interactive and National Health Interview Survey.

<http://www.cdc.gov>

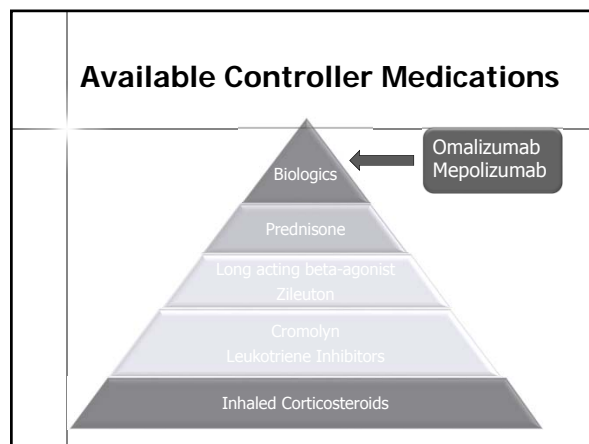
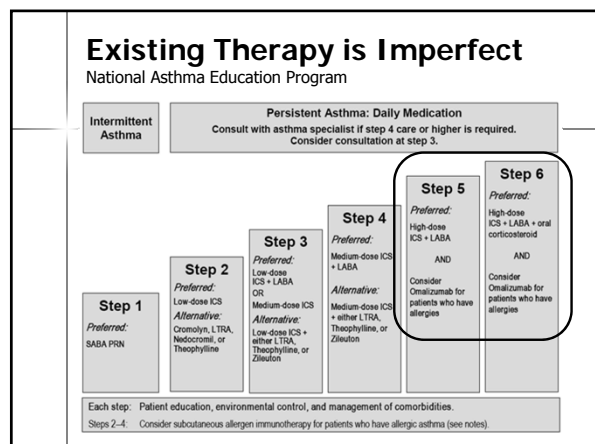
Morbidity Unimproved Over Time: Mortality Improved

Figure 3. Asthma health care encounters per 100 persons with asthma, and asthma deaths per 1,000 persons with asthma: United States, 2001–2009



NOTE: Access data table for Figure 3 at http://www.cdc.gov/nchs/data/asthma/asthma_health_care_2001-2009.pdf.
SOURCES: CDC/NCHS, National Ambulatory Medical Care Survey, National Hospital Ambulatory Medical Care Survey, National Hospital Discharge Survey, National Vital Statistics System, and National Health Interview Survey.

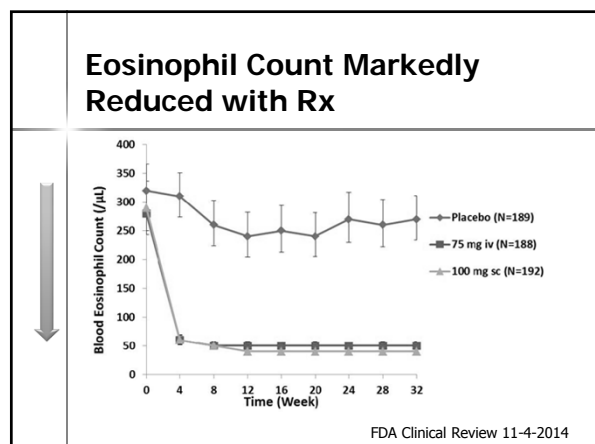
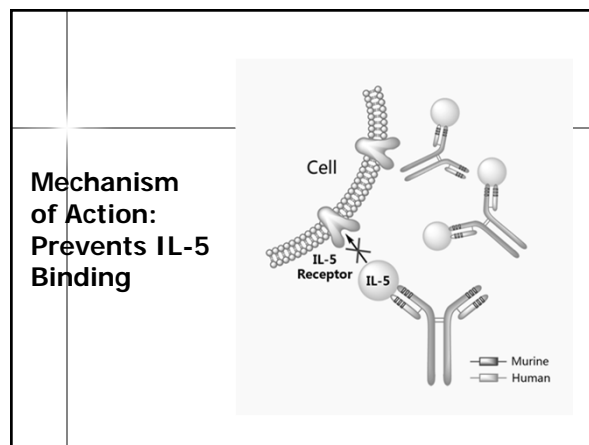
<http://www.cdc.gov>



Mepolizumab is an IL-5 Inhibitor

- Interleukin(IL)-5 promotes growth and activation of eosinophils
- Mepolizumab binds specifically to IL-5 and prevents binding to alpha chain of IL-5 receptors on eosinophils
- Reduces eosinophil activity and survival, and count
- Decreases airway inflammation
- Designed to limit "off target" effects

NEW

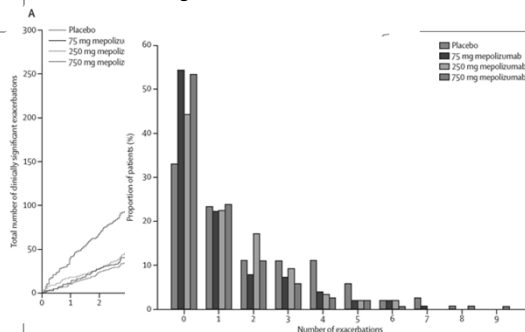


DREAM: Mepolizumab for Severe Eosinophilic Asthma

Lancet 2012;380:651

- 616 patients aged 12-74 with confirmed asthma
- ≥ 2 exacerbations requiring corticosteroids in past year
- Sputum eos > 3%, elevated blood eos, flare after reduction in steroid dose by > 25%
- ATS criteria for refractory asthma on high dose ICS +/- systemic steroids
- Non smokers
- Mepolizumab 75 mg, 250 mg, 750 mg, or placebo IV q 4 weeks

Clinically Significant Exacerbations Reduced by 39-52%



Adverse Events Similar to Placebo



Event (%)	Placebo	75 mg	250 mg	750 mg
Rx withdrawal	4	3	5	6
Fatal event*	0	0	2	1
Headache	17	21	21	21
URI	15	22	22	19
Infusion reaction	6	5	8	12
Hypersensitivity	2	0	1	1

* None thought due to study drug

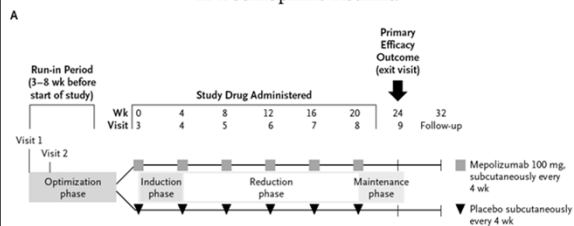
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

SEPTEMBER 25, 2014

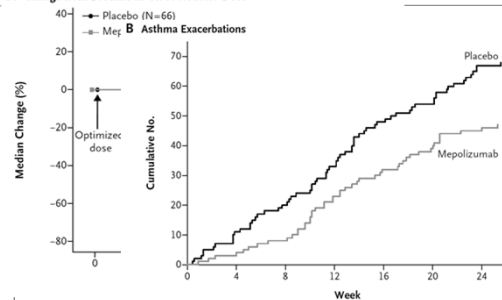
VOL. 371 NO. 13

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

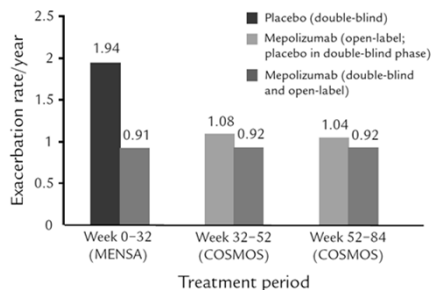


Corticosteroid Dose and Asthma Exacerbations Reduced

A Change from Baseline in Glucocorticoid Dose




COSMOS: Benefit and Safety Maintained at 18 Months



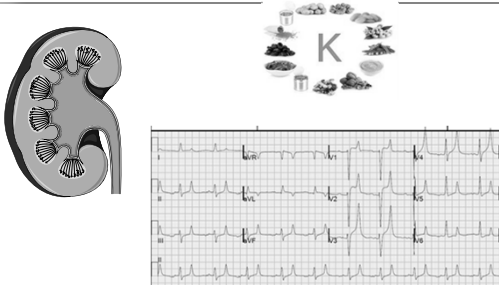
Clin Therapeutics 2016;38:9

Other Considerations


- FDA approved formulation is SC
- FDA indications: add-on Rx to patients with severe asthma and eosinophilic phenotype
- Rare hypersensitivity reactions hours to days after infusion
- Injection site reactions in ~ 8% of patients
- No known drug interactions
- No safety data beyond 18 months

	Key Points 
	<ul style="list-style-type: none"> ■ Reduces exacerbations by ½ ■ Reduce corticosteroid requirement ■ Rare hypersensitivity reactions ■ Eligible population per FDA is vague ■ 100 mg SC q 4 weeks ■ Indications overlap with that of omalizumab (anti-IgE Ab) ■ Single dose costs ~ \$2700 = \$32,500 per year

	What to Advise Mr. Al Buterol?
	<ul style="list-style-type: none"> ■ Estimate eosinophilic phenotype by peripheral eos count ■ Continue other controller medications including LABA +/- LTRI ■ Bribe prior authorization staff... ■ Begin mepolizumab

	Patiromer (Veltassa®) for Rx of Hyperkalemia
	 <p>First Available Jan. 2016</p>

	Ms. Kay Cielle
	<ul style="list-style-type: none"> ■ 55 year old woman ■ Stage 4 CKD / GFR 25 ■ Indication for ACEi but can't tolerate due to hyperkalemia ■ Will this new drug allow me to continue lisinopril? ■ What will it cost me?

	Common Hyperkalemia Scenarios 
	<ul style="list-style-type: none"> ■ Advanced chronic kidney disease ■ CHF with reduced ejection fraction and need for ACEi or ARB ■ Resistant hypertension and need for ACEi or ARB ■ Type IV RTA ■ Indication for spironolactone ■ NSAID requirement

	Existing Options For Rx Limited
	<ul style="list-style-type: none"> ■ Discontinue offending drug ■ Reduce dietary potassium intake ■ Loop diuretics ■ Hemodialysis if more advanced ESRD ■ Sodium polystyrene sulfonate resin (Kayexalate ®)

Sodium Polystyrene Sulfonate: Adverse Events are Substantial

- Binds to and prevents absorption of other meds
- Sodium retention and fluid overload
- Nausea/vomiting
- Intestinal necrosis rarely
- Hypokalemia and hypomagnesemia
- Metabolic alkalosis
- Usually not for use on chronic basis

Patiromer is a Novel Calcium-Sorbitol Polymer



- Non-absorbable polymer
- Exchanges calcium-sorbitol counterion for potassium in GI lumen
- Binding of potassium in gut leads to reduced absorption and serum K⁺ levels

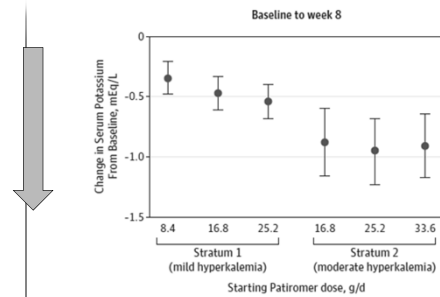
AMETHYST-DN: Effect of Patiromer in Hyperkalemia and Diabetic CKD

- 306 patients aged 30-80
- Type 2 diabetes
- CKD (eGFR 15-60) with or without hypertension
- On ACEi or ARB
- Group 1 mild hyperkalemia 5.0-5.5 mEq/L
- Group 2 moderate 5.5-6.0 mEq/L

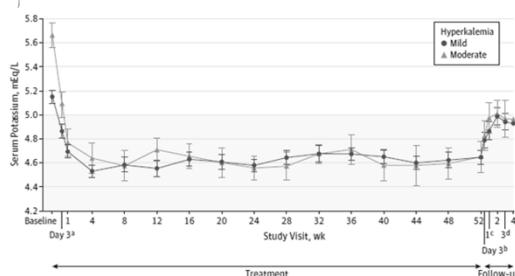


JAMA 2015;314:151

K⁺ Reduced by 0.5-0.9 mEq/L at 8 Weeks



Mean Potassium Levels Normal Through 1-Year of Treatment



OPAL-HK: Patiromer in Patients with CKD and Hyperkalemia while on ACEi/ARB

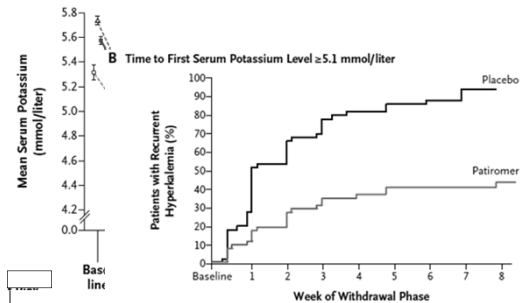
- 243 patients with stage 3-4 CKD
- K⁺ levels 5.1-6.5 mEq/L
- On ACEi (70%) or ARB (38%) for at least 4 weeks
- Excluded patients with EKG changes of hyperkalemia and certain unstable comorbidities
- 4 week unblinded phase followed by 8 week randomized withdrawal phase

NEJM 2015;372:3

OPAL-HK: Baseline Characteristics: High Burden of Comorbidities

Comorbidity	Percent
Type 2 diabetes	57%
Heart failure	42%
Prior MI	25%
Hypertension	97%

Mean K⁺ Values Normalize in < 1 Week: Hyperkalemia Recurs within 1-2 Months of Drug D/C



Adverse Events in Pooled Data are Mostly Minor

Adverse reaction	Incidence %
Constipation	7%
Hypomagnesemia	5%
Hypokalemia	5%
Diarrhea	5%
Nausea	2%
Abdominal discomfort	2%
Flatulence	2%
Hypersensitivity reactions	0.3%

Other Considerations

- In vitro studies: binds ~ one half of all other oral medications tested
- Likely safe in pregnancy (not absorbed)
- No dose adjustment for CKD
- Not studied in acute severe hyperkalemia as emergency Rx
- Can be used chronically
- No studies directly comparing to sodium polystyrene sulfonate

Key Points

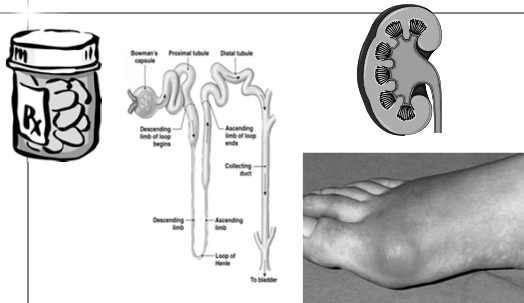


- FDA approved for Rx of non-life threatening hyperkalemia
- Dose range 8.4 to 25.2 grams powder daily
- Administer 6 hours before or 6 hours after all other oral meds. Mix with water
- Do not use if severe constipation, bowel obstruction, or postop ileus
- May allow continuation of ACEI/ARB in CKD or CHF when hyperkalemia occurs on Rx
- Cost for 30 packets = \$595

Advice for Ms. Kay Cielle?

- Can safely continue lisinopril despite moderate hyperkalemia
- Add patiromer
- Titrate dose as needed
- Low potential for important side effects
- Yes, Kay, will be expensive...

Lesinurad (Zurampic®) for the Treatment of Gout and Hyperuricemia



First Available October 2016

Mr. Peau D'Agra

- 50 year old man
- Gout attacks 3-4 times per year
- Loves his lobster and Scotch
- I won't give these up!
- On allopurinol with a uric acid level of 7.2
- Should I add lesinurad to prevent recurrent gout?

Hippocrates

- Gout is the result of an excessive accumulation of one of the bodily humors, probably phlegm
- May result from too rich a diet together with a sedentary life
- Excessive drinking of wine does not actually cause gout
- "Podagra is the most violent of all joint afflictions, it last long, and becomes chronic..."
- "This is a long, painful, but not a mortal illness. If the pain still continues, burn the veins above the joints with raw flax..."

OK, Hippocrates couldn't be right all the time...

W.S. Copeman. A short history of the gout, and the rheumatic disorders. Univ. Calif. Press. 1964

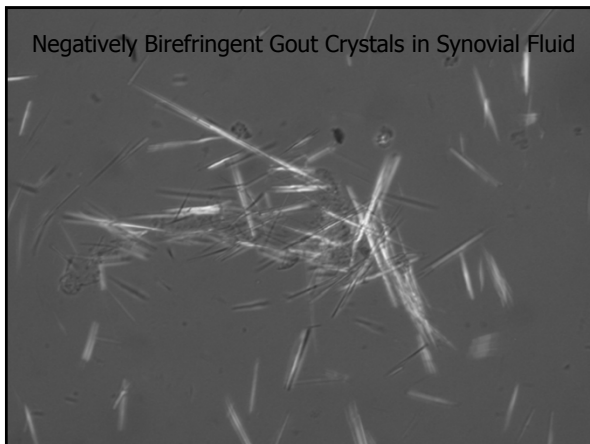
Gout is Common

NHANES III Survey

Arthritis & Rheum 2011;63:3136

	Prevalence	# US Adults (millions)
Gender		
• Male	5.9%	6.1
• Female	2.0%	2.2
Age		
• 20-29	0.4%	0.2
• 30-39	1.3%	0.5
• 40-49	3.3%	1.5
• 50-59	3.7%	1.5
• 60-69	8.0%	2.0
• 70-79	9.3%	1.2

Negatively Birefringent Gout Crystals in Synovial Fluid

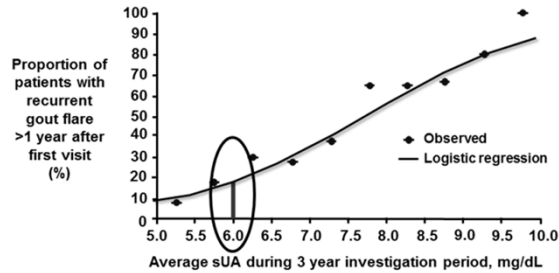


Dietary Recommendation for Patients with Recurrent Gout

Avoid	Limit	Encourage
Sweetbreads, liver, kidney	Shellfish	Low fat or nonfat dairy products
High fructose corn syrup in sodas, food	Beef, lamb, pork	Vegetables
Fruit juices	Table sugar	
Alcohol		

2012 ACR Recommendations for Hyperuricemia. Arthritis Care & Res 2012;64:1431

Association Between Serum Uric Acid Levels and # of Gout Flares



Indications for Uric Acid Lowering Therapy in Gout

- Frequent attacks (>2 per year)
- Tophi
- CKD stage 2 or worse
- Renal stones
- (I add: acute attacks that respond slowly or incompletely to Rx)

2012 ACR Recommendations for Hyperuricemia.
Arthritis Care & Res 2012;64:1431

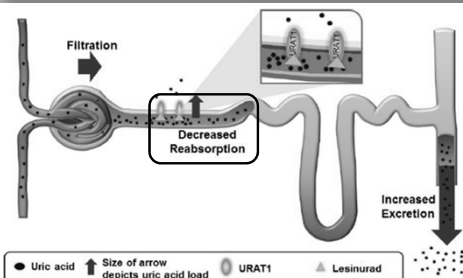
Existing Options to Lower Uric Acid Levels

1. Xanthine oxidase inhibitors
 - Allopurinol ← First line
 - Febuxostat
2. Uricosuric drugs
 - Probenecid
 - Benzbromarone (not available in U.S.)
3. Uricase
 - Pegloticase (porcine uricase infusions)

Lesinurad is a Novel Inhibitor of Uric Acid Transport in Kidney

- Selective inhibitor of:
 - Uric acid transporter 1 (URAT1)
 - Organic anion transporter 4 (OAT4)
 - (No, these are not from Star Wars...)
- Inhibits reabsorption of uric acid in proximal renal tubule
- Causes uricosuria and reduces serum uric acid levels

Lesinurad Blocks Reuptake of Uric Acid from Proximal Tubule

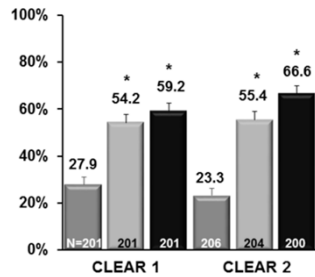


CLEAR 1 & CLEAR2 RCTs of Lesinurad vs. Placebo

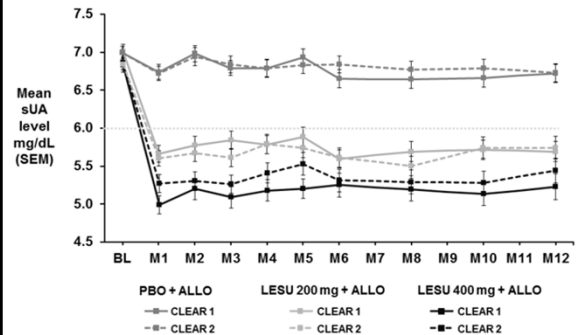
- N = 1213
- At least 2 gout attacks in past year
- On maximum safe dose of allopurinol (300-800 mg qd)
- Randomly assigned to addition of lesinurad 200 mg or 400 mg qd, or placebo
- Primary endpoint serum uric acid level < 6 mg/dl at 6 months

Saag K Arthritis Rheum 2016 (epub)
Dalbeth T Ann Rheum Dis 2016 (epub)

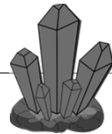
Uric Acid < 6 mg/dl in 55% to 63% of Patients



Reduction in Uric Acid Prompt and Sustained



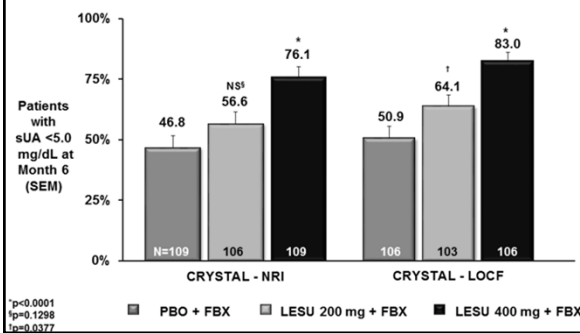
CRYSTAL



- Similarly performed study
- N=324
- All patients on febuxostat
- Randomly assigned addition to lesinurad 200 mg or 400 mg or placebo

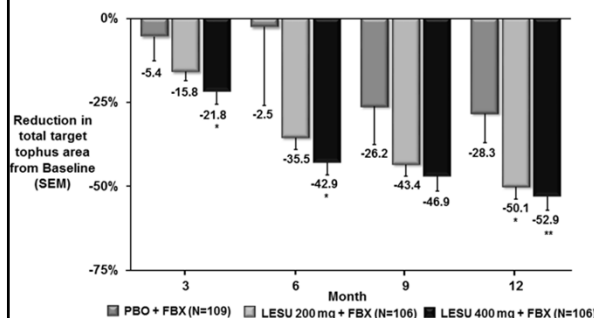
Ann Rheum Dis 2015;74(suppl2): 778

Primary Endpoint Achieved Only for 400 mg Dose



*p<0.0001
†p=0.1298
NS=0.0377

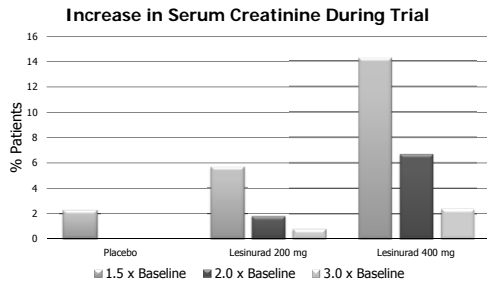
Greater Reduction in Tophus Burden with Combined Rx



Pooled Safety Data: Adverse Events More Common than Placebo Were Minor

Adverse Event	Placebo %	Lesinurad 200 mg %	Lesinurad 400 mg %
Hypertension	4.8	6.1	6.9
Headache	4.1	5.3	5.9
Myalgia	2.1	2.5	3.3
Dizziness	1.4	1.6	2.7

New Serum Creatinine Elevations More Common with Lesinurad



30-Day Cost for Uric Acid Lowering Drugs



Drug	Daily Dose	AWP (USD)
Allopurinol	300 mg	\$8
Febuxostat	40-80 mg	\$285
Probenecid	500-1000 mg	\$45
Lesinurad	200 mg	\$350

Other Considerations

- Most (2/3) creatinine elevations resolve despite continuing drug
- AKI more common when given as monotherapy without allopurinol
- No increase risk of renal stones
- Drug interactions: CYP2C9 metabolism
- FDA Black Box warning: Do not use as monotherapy without allopurinol**

Key Points






- Single daily oral dose 200 mg daily
- More than 1/2 of patients achieve uric acid < 6 mg/dl
- Do not use for patients with eGFR < 40
- Monitor renal function while on Rx
- Mild to moderate increase in creatinine common; less frequent with FDA approved 200 mg dose
- Generally otherwise well tolerated
- Do not use as monotherapy without allopurinol

Mr. Peau D'Agra

- Continue allopurinol
- Lay off the lobster
- Cut back on the wine
- If uric acid > 6 mg/dl, then add lesinurad
- Monitor renal function

Scorecard for Our Patients

		
Mepolizumab	Patisomer	Lesinurad
		

	Summary
	<ul style="list-style-type: none"> ■ Mepolizumab reduces steroid dose and asthma exacerbations but is expensive ■ Patiromer is safe long term Rx for hyperkalemia due to ACEi/ARB or CKD ■ Lesinurad in combination with allopurinol achieves target uric acid in most patients

	A Final Thought...
	<p>"For some patients, though conscious that their condition is perilous, recover their health simply through contentment with the goodness of their physician."</p> <p>Hippocrates (460-375 BC)</p>