Gout and its place in world history

[Timeline]

- David Wells 15th perfect game in Major League history
- Benjamin Franklin co-drafted Declaration of Independence
- Henry VIII King of England 1509-1547

Gout and its place in ancient history

“Persons affected with the gout who are aged, have tophi in their joints, who have led a hard life, and whose bowels are constipated are beyond the power of medicine to cure” – Hippocrates c. 400 BCE

Gout and its place in prehistory

The New York Times

May 22, 1997

Pity a Tyrannosaur? Sue Had Gout

By MALCOLM W. BROWNE

For all the suffering she probably caused her Cretaceous prey, a tyrannosaur named Sue seems to have paid dearly. Scientists have determined that the big dinosaur probably was a victim of agonizing gout and other debilitating ailments.
Why give update on gout at Advances in Internal Medicine?

1. Gout is prevalent: 2007-2008 NHANES 3.9% (8.3 million)\(^1\)
   - Men = 5.9% (6.1 million)\(^1\)
   - Women = 2.0% (2.2 million)\(^1\)
   - Prevalence has increased by 1.2 percentage points (30%) in past two decades\(^1\)
   - Crystalline arthritis accounted for 2.3% (39 million) admissions\(^2\)
   - Gout responsible for 5% (5 million) outpatient visits 2010\(^2\)

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Why give update on gout at Advances in Internal Medicine?

In 2002, What percentage of outpatient visits specifically for gout were to rheumatologists?

A. 1.3%
B. 13%
C. 33%
D. 53%
E. 73%

---

Why give update on gout at Advances in Internal Medicine?

In 2002, What percentage of outpatient visits specifically for gout were to rheumatologists?

A. 1.3%
B. 13%
C. 33%
D. 53%
E. 73%

2. Gout is treated primarily by PCP’s in U.S.

   - Only 1.3% of all outpatient visits for gout treated by rheumatologists\(^3\)
   - 70% of patients with gout are under the care of primary care physicians
   - Only 3% of gout patients are referred by PCP’s to rheumatologists

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Why give update on gout at Advances in Internal Medicine?

3. Gout is generally mismanaged
   - Underuse of uric acid lowering therapy (ULT) in eligible patients likely to benefit
   - Under-dosing of allopurinol in patients on ULT (40% with serum uric acid ≥6 on current dose)
   - Initial overdosing of allopurinol in some patients at risk for hypersensitivity

4. Plethora of urate lowering therapies currently available or coming to market

Gout in recent general medical literature

ACP Guidelines 2017: Extraordinary disappointment
Gout guidelines published by rheumatology societies

US: ACR 2012

Europe: EULAR 2016

Acute Gout

- Acute, usually self-limited monoarticular inflammatory arthropathy
- Inflammatory response directed against monosodium urate crystals in synovium
- Usually but not always associated with hyperuricemia
- Monosodium urate crystals precipitate around at a concentration of 6.8 mg/dL, within reference range in most US populations

Distribution of Serum Uric Acid Levels in Japan: 34,000 People

Normal = Mean + 2SD

Clinical Significance
Serum uric acid measurements are useful in the diagnosis and treatment of numerous renal and metabolic disorders, including renal failure, gout, leukemia, prostate, starvation or other wasting conditions, and in patients receiving cytotoxic drugs.
Acute Gout Diagnosis

- **Definitive:** Crystal Identification – the only way!
  - Joint fluid examination under polarized microscopy with red compensator
  - Strongly negatively birefringent needle shaped crystals
- **Suspected:** Characteristic radiographic “gouty” corticated erosions away from joint space
- **Possible:** Classic clinical picture with elevated serum urate
- **However –** presence of hyperuricemia alone is not diagnostic of gout

Therapy for Acute Gouty Flares

- Acute gout attacks are often self-limited (3-5 days)
- **Goals:** reduce both severity and duration of attack
- **NSAIDs**
  - Effective and rapid relief of symptoms
  - Contraindicated in patients with GI, Renal, or hypersensitivity concerns
- **Corticosteroids** (intra-articular and/or systemic use)
- **Colchicine:**
  - Low dose only (0.6 mg BID)! Not every hour until patient gets sick
  - Must be used within 48 hours of attack onset (blocks leukocyte migration)
  - Likely not as effective as either NSAIDs or corticosteroids

Colchicine: How Effective for Acute Gout??

![Table 2: Efficacy analysis (micro-escue population, n = 194)](image)

<table>
<thead>
<tr>
<th>Treatment response based on target</th>
<th>Colchicine dose</th>
<th>Placebo dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain at 12 hours after first dose</td>
<td>17 (77.5)</td>
<td>20 (72.7)</td>
</tr>
<tr>
<td>Pain at 24 hours after first dose</td>
<td>19 (76.5)</td>
<td>21 (74.1)</td>
</tr>
<tr>
<td>Pain at 48 hours after first dose</td>
<td>19 (76.5)</td>
<td>22 (74.2)</td>
</tr>
</tbody>
</table>

Fewer than 40% of patients achieve primary endpoint
High dose no more efficacious and more toxic

Managing Chronic Gout: 2012 ACR Guidelines

![Guidelines image](image)
Question I

55 year old male with a history of known gout awakens with right knee pain and swelling one morning that worsens over next 48 hours until he has difficulty walking on that knee. On a recent Chem. 20 panel, uric acid level was elevated at 10.7. He denies any other joint pains, IVDU, or recent sexual contacts.

After undergoing arthrocentesis confirming the diagnosis of gout and ruling out an infectious process, the patient is started on indomethacin and allopurinol 300 mg/day and sent home. Which of the following actions in this case was a mistake?

A. Allopurinol dose
B. Indomethacin therapy
C. The patient was not admitted and treated with antibiotics until synovial fluid cultures were negative for 5 days
D. Use of allopurinol during acute phase of gout

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Chronic Gout - Progression

More frequent inflammatory arthritic attacks
  - Monoarticular attacks
    - Same joint
    - Spread to other joints
  - Polymarticular attacks of arthritis as disease progresses

Attacks blend together/ No longer completely self-limited

Chronic synovitis resembling rheumatoid arthritis

Destructive arthritis/Tophaceous gout:
  - Uric acid containing tophi deposit in joints/tendons/soft tissues, can lead to erosions and deformities

Chronic Gout – 2012 ACR guidelines

Goal: Treat to target uric acid level
  - Lower serum uric acid levels are associated with fewer attacks
  - Target serum urate levels below crystallization concentration (< 6.0 or even 5.0 in severe gout) to reabsorb tophi and remove UA stores
  - 1st line Uric acid lowering therapies: allopurinol and Febuxostat
  - Other therapies now available to get uric acid levels to target for patients who fail or are contraindicated/intolerant to 1st line meds

Prophylaxis
  - Prophylaxis against acute gout flares when initiating or adjusting uric acid lowering therapy (Europeans recommend six months)
  - Colchicine does work well for this (0.6 mg/day usually suffices)
  - NSAIDs and prednisone work as well
Treating hyperuricemia: ACR 2012 guidelines

- Do not treat asymptomatic hyperuricemia
  - primary hyperuricemia may someday be linked to cardiovascular or metabolic syndromes
- General goal is:
  - To reduce frequency and severity of subsequent attacks of gout
  - To resorb tophaceous uric acid deposits that can cause joint damage
- Allopurinol and febuxostat are considered first-line therapies for hyperuricemia associated with gout
- It’s now considered acceptable to initiate urate-lowering therapy during acute flares provided adequate treatment of flare is begun and prophylaxis against future flares is maintained for at least three months after flare

ACP Guidelines: Key failure

- The ACP expert panel couldn’t bring itself to recommend treating to a serum uric acid target
- Cited lack of evidence to recommendation (formal randomized prospective trials comparing treating to specific target on outcomes of gout flares, tophus reduction, metabolic syndrome, etc...)
- Cited clinical trials of urate lowering therapy with increased gout flares (lacked adequate prophylaxis)
- Ignored its own cited mountains of other literature/evidence (2 RCTs post-hoc analysis and 8 retrospective cohort studies) supporting long term reduction in gout flares and complications of hyperuricemia with treatment to serum urate <6 and better if <5.
- Ignored common sense: "The guideline......imperils good outcomes, and could set optimal treatment of the disease back decades." – R. Turkeltaub MD UCSD

Addressing co-morbid conditions in gout patients with hyperuricemia

Non-pharmacologic treatments for hyperuricemia

- Patient education about hyperuricemia, diet, and lifestyle modifications
- Consideration given to uric acid-elevating medications
  - Key culprits are thiazide and loop diuretics, niacin, and cyclosporine
  - Obviously if drug benefits outweigh small improvement in uric acid, then do not adjust or discontinue
A 62 YO male patient of yours with gout comes to your office asking what dietary changes he should make in helping to treat his gout and hyperuricemia. According to the ACR guidelines, you recommend that he avoid which of the following?

A. Modest alcohol intake
B. Foods and beverages with high fructose corn syrup
C. Chicken and turkey
D. Low fat dairy products

**Diet recommendations:**
**Fairly Meager evidence**

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Limit</th>
<th>Encourage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>high-purine content (e.g., sweetbreads, liver)</td>
<td>B</td>
</tr>
<tr>
<td>High-fructose corn or maize sweetened sodas, soft drinks, or foods</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Alcohol (not over 1 oz per day) in a male and 0.5 oz per day for a female is all good products.</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Any alcohol is increased risk in patients with gout.</td>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>

Khanna et al. Arth Care and Research 2012: 64;10 1431-1446

**Chronic Gout: Uric Acid Lowering Therapies**

- **Allopurinol**
  - Xanthine Oxidase Inhibitor (blocks metabolism of purines to uric acid)
  - Effective for both under-excreters and overproducers of uric acid
  - Now acceptable to start many gout patients on allopurinol during a flare if they are responding appropriately to anti-inflammatory agents
  - Don’t stop therapy during an acute attack
Allopurinol is purine derivative: a dead ringer for hypoxanthine

Allopurinol competes with Hypoxanthine for xanthine oxidase

Purine Metabolism

Using allopurinol properly

- Do not start patients on more than 100 mg/day
- Dose reduce ALL patients with moderate to severe renal insufficiency
- Gradually up-titrate the dose, which in some cases, can be more than 300 mg/day if needed
- Treat to Target: serum urate concentration <6 if treating tophi, and <5 ideally.
- Push the allopurinol dose over 300 mg/day if necessary!!

EULAR 2016 Treat to Target Recommendations

Table 2: Recommendations to treat to target urate

<table>
<thead>
<tr>
<th>target</th>
<th>Colchicine</th>
<th>Uric Acid</th>
<th>Allopurinol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>1,5 6,1</td>
<td>2,5 6,1</td>
<td>1,5 6,1</td>
</tr>
<tr>
<td>Goal</td>
<td>1,5 6,1</td>
<td>1,5 6,1</td>
<td>1,5 6,1</td>
</tr>
<tr>
<td>Total</td>
<td>1,5 6,1</td>
<td>1,5 6,1</td>
<td>1,5 6,1</td>
</tr>
</tbody>
</table>

Recommendations:
1. Colchicine should be used for patients with a high initial urate content and who are at risk of gout flare.
2. Allopurinol should be used for patients with moderate to severe renal insufficiency.
3. Uric acid inhibitors should be used for patients with mild to moderate renal insufficiency.
4. Etanercept should be used for patients with severe gout.
5. Acetaminophen should be used for patients with moderate to severe renal insufficiency.
6. Colchicine should be used for patients with severe gout.
7. Uric acid inhibitors should be used for patients with mild to moderate renal insufficiency.
8. Etanercept should be used for patients with severe gout.
9. Acetaminophen should be used for patients with moderate to severe renal insufficiency.

EULAR 2016 Treat to Target - Recommendations
Allopurinol Toxicities

- Careful use in patients with renal failure
  - Metabolites are renally cleared
  - Hypersensitivity reactions are more common in patients with renal insufficiency
- Purine-associated hypersensitivity syndrome is DIFFERENT from allergic rash
  - Systemic and sometimes life threatening illness
- Fever, Steven's-Johnson/TEN, hepatitis, marrow suppression, nephritis, DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) The Role of HLA 5801 and Allopurinol Hypersensitivity is unquestioned
- All patients from populations with a high allele frequency for HLA 5801 and high hazard ratio for developing hypersensitivity should be screened!!

HLA B5801 and Allopurinol Hypersensitivity
Hung et al. PNAS 2005

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Allopathic Control</th>
<th>P value*</th>
<th>Allopathic Hypersensitivity</th>
<th>P value*</th>
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<tbody>
<tr>
<td>B5801X1</td>
<td>110/1250</td>
<td>0.005</td>
<td>10/1250</td>
<td>0.001</td>
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<tr>
<td>A*0201</td>
<td>24/1052</td>
<td>7.4</td>
<td>4/1052</td>
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<tr>
<td>A*0101</td>
<td>22/1052</td>
<td>10.5</td>
<td>2/1052</td>
<td>0.001</td>
</tr>
<tr>
<td>A*0102</td>
<td>22/1052</td>
<td>10.5</td>
<td>2/1052</td>
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*P values were adjusted by using Bonferroni's correction for multiple comparisons to account for the observed alleles.

1. B5801 confers nearly 600 fold increased risk of allopurinol hypersensitivity
2. Allele and association is particularly important in Han Chinese patients, Thai, and Korean patients

Allopurinol Pharmacogenetics
Bench Clinic

The Present State of Gout Therapy: What to do with a More Challenging Case?

You are seeing a 56 year old male with long standing diabetes, hypertension, chronic renal insufficiency, and destructive tophaceous gout. His gout originally began as episodic podagra that became more frequent and involved more joints over time. In the past few years, his tophi have grown larger and more numerous, and acute episodes of inflammatory arthritis have begun to blend together into a chronic, painful, polyarticular inflammatory synovitis in his hands, elbows, knees, and feet from which he has come to your office seeking relief.
Gout: Findings

- He has chronic swelling, synovitis, and deformities reminiscent of rheumatoid arthritis
- Numerous tophi scattered on arms, legs, and ears
- Serum creatinine is 1.8
- Uric Acid 10.2

Managing the Chronic Disease

Which of the following options is best suited to treat his hyperuricemia to target:

A. Starting allopurinol 300/day
B. Colchicine 0.6 mg/day
C. Probenecid 250 mg twice daily
D. Start febuxostat 40 mg/day

Managing the Chronic Disease

Which of the following options is best suited to treat his hyperuricemia to target:

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D. Start febuxostat 40 mg/day

Difficult to manage chronic gout

- Generally do not start 300 mg/day of allopurinol on most patients, especially with chronic kidney disease
- Mechanism of colchicine doesn't treat hyperuricemia
- Probenecid won’t work without adequate GFR and is contraindicated in tophaceous gout anyway
- Starting very low allopurinol (50mg or 100 mg QOD and titrating up is an option, but febuxostat is effective and safe in patients with moderate CKD
Febuxostat (FDA approved 2009)

- First treatment in 40 years for chronic gout
- NON-PURINE inhibitor of xanthine oxidase
- Theoretically safe to use in patients with allopurinol reactions
- Been studied in patients with mild renal insufficiency
- Dosed at 40-80mg/once daily

Fubuxostat is Not a Purine

Comparison of Febuxostat to Allopurinol
Becker et al. NEJM 2005

- 80mg and 120 mg of febuxostat superior to allopurinol 300mg/day
  - Percent of patients achieving uric acid <6
  - Greater reduction in serum uric acid levels
- Safe in patients with mild-moderate renal insufficiency (SCr ≤1.5 in this study) and patients with previous allopurinol reactions
- Note: Allopurinol 300/day is probably suboptimal dose for many patients
Febuxostat: Summary

- More potent than 300 mg/day allopurinol (but many patients can tolerate higher doses of allopurinol)
- As it is not a purine: Appropriate for patients with allopurinol hypersensitivity
- Can be used safely in patients with mild renal insufficiency (unlike allopurinol)

Treating severe, refractory tophaceous gout

Lifetime of standard uric acid lowering treatment won’t eliminate these tophi

Uricase

- Enzyme that converts insoluble uric acid to more soluble metabolite allantoin
- Most of animal kingdom (& many mammals) possess uricase, but not humans have lost gene function
- Rasburicase: a drug derived from aspergillus used to treat tumor lysis syndrome in pediatric leukemia
- Rasburicase is extremely immunogenic, which limits its half life and use in chronic diseases

Pegloticase (FDA approval Sept. 2010)

- Mammalian uricase
- Pegylated
  - Increases half life
  - Reduces immunogenicity
- Administered by IV infusion every 2 weeks
Efficacy of Pegloticase
Sundy et al. A&R 2008

- Phase 2 randomized open label dose ranging study 41 patients with serum urate >8
- Intolerance or inadequate response to standard urate lowering therapy (UA>6) for at least 3 months
- Plus one of the following:
  - At least one tophus
  - At least one flare in last 6 months
  - Chronic gouty arthropathy

Visible Results

A

B

C

D

Before Treatment

After Treatment

Efficacy of Pegloticase
Phase 2 (12 week) open label dosing trial 41 patients

Purine Metabolism

Nature Reviews | Drug Discovery

Phase 2 randomized open label dose ranging study 41 patients with serum urate >8
Intolerance or inadequate response to standard urate lowering therapy (UA>6) for at least 3 months
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- Chronic gouty arthropathy

Visible Results

A

B

C

D

Before Treatment

After Treatment
Pegloticase: Not holy grail

- Adverse events:
  - Infusion reactions (not human, even with PEG)
  - Many patients develop antibodies to drug that increases its clearance and reduces its efficacy
  - Anaphylaxis
  - 80% patients had gout flares despite prophylaxis
  - Contraindicated in G6PD deficient patients
  - May exacerbate CHF

Pegloticase: Summary

- Effective agent for acute lowering and chronic reduction in serum uric acid levels
- Serum uric acid levels are low enough in some patients to promote tophus resorption
- Medication is expensive, immunogenic, and associated with adverse events
- Refer these patients with severe tophaceous gout to rheumatologists!!

Renal excretion of uric acid

Hyperuricemia

Chronic Gout: Uricosuric agents

- Probenecid: An old friend
  - Uricosuric agent blocks tubular re-absorption of uric acid
  - Useful in patients who under-excrete uric acid (90%)
  - If need be, confirm under-excretion with 24 hr. uric acid <800 mg/24 hrs.
- Do not use if:
  - Tophi
  - Renal insufficiency
  - Clear overproduction syndrome
Target #1: URAT 1
Enhancing Uric Acid Elimination


Lesinurad

- FDA approved 2016 uricosuric for use in combination with xanthine oxidase inhibitor (allopurinol or febuxostat) to lower uric acid
- Useful add-on therapy in treat to target scenario
- Similar contraindications and limitations to probenecid in kidney disease (use with allopurinol is required)

Effectiveness of Lesinurad as add-on to Allopurinol in treat to target

Saag et al. Vol. 69, No. 1, January 2017, pp 203–212

CLEAR 1 (N=603) and CLEAR 2 (N=610), 91% and 84% were receiving allopurinol 300 mg (range: 200-900 mg) daily

Advances in Therapies for Gout: Summary

- Gout is an ancient disease for whom modern therapy is finally available
  - Should be managed effectively by internists and PCPs who use treat to target approach (not in ACP guidelines)
- New therapies are available
  - Febuxostat (allopurinol refractory, intolerant, or contraindicated)
  - Pegylated uricase: severe tophaceous disease
  - Novel uricosuric agents like lesinurad
- Rheumatology referral appropriate for difficult to manage cases
The future is bright for those with gout who do not go extinct

Back to our Challenging Case....

- He has chronic swelling, synovitis, and deformities reminiscent of rheumatoid arthritis
- Numerous tophi scattered on arms, legs, and ears
- Serum creatinine is 1.8
- Uric Acid 10.2
- Diabetes

Managing the Acute Symptoms

In the acute setting, the best approach to managing this patient's symptoms would be to start:

A. Indomethacin 75 mg-100mg PO TID
B. Colchicine 0.6 mg PO q2hr until he improves
C. Prednisone 20 mg PO QD
D. Allopurinol 300 mg PO QD
### Managing the Acute Symptoms

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D. Allopurinol 300 mg PO QD

### Managing the Acute Symptoms

A. Indomethacin 75 mg-100mg PO TID
   - Can’t use because of renal disease
B. Colchicine 0.6 mg PO q2hr until he improves
   - Not standard of care for acute gout
C. Prednisone 20 mg PO QD
   - Best choice, but not ideal given diabetes
D. Allopurinol 300 mg PO QD
   - Not used to treat acute inflammation

Are there any anti-inflammatory treatments on the horizon for those refractory to or intolerant of standard therapy??

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### Therapy for Acute Gout: A “Biologic” Future??

**Target #2: The Inflammasome**

**Gout pathogenesis:**
- Super saturated serum levels of uric acid lead to crystal formation and deposits in joints
- Crystals are engulfed by macrophages
- Macrophages release inflammatory cytokines
- Recruit more inflammatory cells and perpetuate joint inflammation

How do inert UA crystals lead to inflammation?

---

### How does uric acid lead to inflammation??

- **Innate Immune System:**
  - Inflammatory cells can innately recognize common microbial features as danger signals
    - Flagella, viral RNA, etc...
  - Leads to rapid inflammation (even septic shock) that acts as “speed bump” until adaptive immune response kicks in
  - Microbial patterns bind to Toll-like receptors and lead to production of pro IL-1
IL-1 Production

• Pro-IL-1 is inactive, but capable of being rapidly metabolized to active IL-1

• Machinery that cleaves pro IL-1 to active IL-1 is called the inflammasome and is induced by a second required danger signal

• Uric Acid is capable of activating the inflammasome

Dual activation of pattern receptors PLUS a host danger signal (Uric Acid)

Inflammation

Is IL-1 Blockade Effective for Gout?

• IL-1 blockade via
  – IL-1 Receptor antagonist (Anakinra, commercially available for Rheumatoid Arthritis)
  – Anti IL-1 antibody (Canakinumab, commercially available to treat certain periodic fevers)
  – IL-1 decoy receptor fusion protein (Rilanocept, commercially available to treat certain periodic fevers)

• Several pilot studies suggest these all work!

• Single dose of Canakinumab superior to triamcinolone injection (has long half life)
Canakinumab (CK) vs. Triamcinolone
So et al. A&R 2010

- CK administered as one of 5 single doses
  - Previous gout flare
  - Acute gout flare <5 days
  - Inability to take other acute gout therapy

- Primary endpoint: find dose of CK equivalent to triamcinolone for reduction of pain at 72 hours

- No equivalent dose! All canakinumab doses superior to triamcinolone at 72 hours

Time to First Gout Flare
So et al. A&R 2010

Secondary endpoints:
- 8 week reduction in gout flares
- Time to 50% reduction in pain
- Reduction in serum inflammatory markers
- Patient and physician global assessments
- Use of other gout therapies

Not Quite Ready for Prime Time

FDA rejects expanded use of Regeneron drug for gout
Published July 31, 2012
Reuters
Regeneron Pharmaceuticals Inc said U.S. regulators have denied approval for it to expand use of its Arcalyst drug to prevent gout flares, asking that the company provide more clinical data.
The rejection follows a unanimous vote against the drug's approval in early May by advisors to the U.S. Food and Drug Administration, with panel members expressing concern that the company had only done a 16-week study.

FDA Panel Votes Against Gout Drug
By THOMAS M. BURTON
WASHINGTON—The Food and Drug Administration is grappling with the novel question of whether a Novartis AG NVS +0.97% gout-pain drug should be marketed when patients receiving just one injection had a higher rate of serious infections in clinical studies.
An FDA advisory committee Tuesday voted 11-1 against approving the drug, called ilaris, because of the safety concerns.