GOUT – THE MOST COMMON INFLAMMATORY DISEASE

News from the World Congress of Internal Medicine 2018, Cape Town

Introduction

“Gout is a well-known entity, but it is still poorly managed,” said Professor Brian Mandell, specialist physician, Cleveland Clinic, speaking at the WCIM 2018 Congress in Cape Town. In his presentation, he provided advice on the appropriate use of available therapies to minimise the discomfort and deformities associated with this ancient inflammatory condition.

The most important clinical concept when initiating treatment is the understanding that gout is a metabolic deposition disease and that a painful attack of gout is a symptom of the disease and not the disease itself.1,2

KEY MESSAGES

• An attack of gout is a symptom of an ongoing metabolic disease of uric acid deposition
• Urate-lowering therapy should seek to cure the condition
• Prophylaxis with colchicine/NSAIDs is essential for at least six months when urate-lowering therapy is initiated
• Gout warrants more clinical attention as it occurs with life-threatening comorbidities.
What is gout?

Gout is a metabolic disease of uric acid deposition; it occurs when the saturation concentration of urate reaches approximately 6.8mg/dl in physiological fluids. Saturation is influenced by temperature, so clinical symptoms typically occur first in distal joints – the big toe (metatarsophalangeal joint– MTP1) and heels, ankles and knees; the symptoms are caused by the needle-like deposition of monosodium urate (MSU) crystals in the synovial space. Gout is a disease of reversible, chronic unwanted uric acid deposition.

Why is gout on the increase?

Three factors play a key role in the increasing incidence of gout:

- Dietary changes
- Obesity and the metabolic syndrome
- Increasing age.

Diets rich in meat, seafood, fructose-containing drinks and beer are major contributory factors. These purine-rich foods contribute to uric acid overproduction via the purine metabolic pathway. Alcohol, particularly beers and ales, also contribute to hyperuricaemia, as does excessive calorie intake.

Ageing impacts on renal function, leading to decreased uric acid excretion. Hypertension and treatment with thiazide and loop diuretics can also contribute to hyperuricaemia.

What predicts gout?

Serum uric acid (SUA) levels predict the likelihood of an initial flare-up of gout, but raised levels do not always precipitate gout symptoms in all individuals. For both gout incidence and recurrence, a graded trend has been observed in published cohort studies where the risk is increased with higher SUA levels. Recurrent gout risk in these clinical cohorts ranged from 12% (SUA ≤6mg/dl) to 61% (SUA ≥10mg/dl) in patients receiving antihyperuricaemic therapy. This stresses the importance of effective urate-lowering therapy (ULT) in persons who have already experienced an attack of gout.

Repeat attacks, when on ULT, are often due to mobilisation of crystals and the lengthy time it takes (1-3 years) to lower the average serum urate and the occurrence of gout flares.

Will lowering SUA levels reduce flares?

Two important studies reflect the clinical reality of effective uric acid lowering strategies. In a New Zealand study, 314 patients with early gout (one or two flares in the past year), SUA levels higher than 7mg/dl and no renal impairment were given a xanthine oxidase inhibitor (XOI) and colchicine 0.5mg once daily or naproxen 250mg twice daily as prophylaxis against gout flares for two years. The XOI therapy (in this instance, febuxostat) improved the synovitis score, decreased the overall incidence of gout flares and improved SUA control.

In a second American study, 760 patients were treated with either allopurinol (200-300mg) or febuxostat (80-120mg) to reduce SUA levels to less than 6mg/dl; this proved to be an effective target level for achieving very significant reduction in flares (Figure 1). “From these studies it is evident that treatment needs to target lower levels than normally thought necessary and needs to be lengthy, and even life-long, to prevent attacks.”

Evidence for life-long therapy comes from a Spanish study which showed that after stopping five-year ULT, flares occur in 30% of patients within the following four years.4 “We need to manage gout in the same way we do coronary artery disease (CAD), with chronic treatment to lower risk of a further event.”

“Gout is a disease of reversible, chronic unwanted uric acid deposition.”
"We need to manage gout in the same way we do CAD, with chronic treatment to lower risk of a further event."

Management of gout

The importance of follow-through therapy after an acute attack is well substantiated and it should seek to achieve therapeutic remission; ‘a cure in fact’ (Figure 2). The point where ULT should be introduced is defined in numerous guidelines and it should be started in patients who experience two or more attacks per year, where there is renal impairment (lowering urate is renoprotective) or the presence of urate stones, tophi or x-ray evidence of erosions. In all instances, therapy should be individualised.

Why is current management suboptimal?

The real issue is suboptimal dosing: the allopurinol dose is commonly not up-titrated to achieve target SUA levels over time. Patient education helps and awareness of occasional drug resistance or hypersensitivity (1-2/1000 patients per year), which may require switching to another XOI, is important. This suggests that regular monitoring of SUA levels is required.
What is the correct dose of allopurinol?

Most clinicians believe 300mg is effective, but this is not true; this dosage is only effective in the 30% of patients who reach the required target SUA levels.

The value of up-titration was investigated in the FAST trial where 400 patients over the age 60 years with eGFR >30ml/minute were treated to target SUA levels <6mg/dl. The effective treatment-to-target dosage was 100-700mg daily, leading to a useful clinical concept that for each 100mg of allopurinol therapy, a SUA level drop of 1mg/dl will be achieved. Successful approaches to ULT are defined in Table 1.

What about treating chronic kidney disease patients with allopurinol?

Does the dose need to be reduced? Twenty percent of gout patients also have chronic kidney disease (CKD) and allopurinol hypersensitivity is more likely to occur in these patients (2-4/1000 people) and in those with HLA-B*5801. Despite this, there are no hard data that dose reduction in patients with CKD prevents hypersensitivity. A pragmatic approach to these patients is outlined in Table 2.

What about other medications and serum urate levels?

While aspirin (81mg) raises serum urate, it only results in a 0.3mg/dl increase and should not be stopped if needed for secondary cardiovascular disease risk reduction. A hydrochlorothiazide (HCTZ) diuretic at a 25mg dose causes an increased urate level of 0.78mg/dl; this should be considered and other effective antihypertensive therapy introduced. Alternatively, the allopurinol dose can be increased. “In my view, the clinician almost never has to stop aspirin or HCTZ.”

---

**Table 1: Successful urate-lowering strategies in the office**

- Establish goals and objectives of therapy
  - Discuss with the patient
  - Describe likely and serious side effects
  - Plan to treat to a target SUA
  - Establish simple SUA monitoring plan
  - Adjust the medication dose (~ q2 weeks)

- Educate
  - Rationale for approach to therapy
  - Time course of therapy
  - Provide an approach to managing flares
  - Stopping/starting medications (don’t stop ULT)

**Table 2: ULT in patients with CKD (Professor Brian Mandell’s opinion)**

- Start allopurinol at low does: ~50mg
  - Minimise flares, possibly minimise hypersensitivity

- Increase dose with monitoring of SUA levels to reach target of ≤6.0mg/dl; <5mg/dl if there are palpable tophi
  - Minimal safety data for this approach
  - Almost no data against it

- Consider checking HLA-B*5801 (high percentage in Han Chinese) – low prevalence in Europeans – increased risk of hypersensitivity reactions
  - Hypersensitivity in Taiwan: 4.7/1000 patients (~20% are 5801+)
  - 2/1000 hospitalised
  - Rate reduced to 0 hospitalised if not given to HLA-B*5801 patients

- Or use febuxostat – start 20mg (off label, cut 40mg pill) increase dose to reach target SUA levels (FDA max: 80mg)


Treating the symptoms of gout – prevention and management of the acute flare

It is important to understand that attacks can occur as long as urate deposits exist around joints, tendons or bursae. Attacks can also be precipitated by fluctuations in serum urate levels that typically occur on initiation of ULT. The greater the sudden decrease in SUA levels, the more likely the patient is to have an attack. Management strategies are summarised in Tables 3 and 4.

<table>
<thead>
<tr>
<th>Table 3: Preventing acute flares with initiation of ULT – Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Colchicine – effective – continue for ~ 6 months (or until palpable tophi gone)</td>
</tr>
<tr>
<td>- Qd – bid as tolerated (gastrointestinal issues)</td>
</tr>
<tr>
<td>- Beware neuro- and myotoxicity – dose adjust and monitor closely with any CKD</td>
</tr>
<tr>
<td>- Beware of drug interactions</td>
</tr>
<tr>
<td>- Withhold chronic colchicine when adding clarithromycin</td>
</tr>
<tr>
<td>• NSAIDs – all probably work</td>
</tr>
<tr>
<td>- Little data ± trial data with 250mg bid naproxen</td>
</tr>
<tr>
<td>- There is some concern about side effects</td>
</tr>
<tr>
<td>• Steroids – not ideal (side effects and may not work – transplant experience)</td>
</tr>
<tr>
<td>• Anti-interleukin (IL)-1-directed therapies – dramatically effective, expensive, no FDA approval (approved in Europe)</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Table 4: Managing acute flares</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Colchicine</td>
</tr>
<tr>
<td>- 1.0mg then 0.5mg reduced pain by 50% after 24 hours; may not resolve attack</td>
</tr>
<tr>
<td>- 30% of patients in randomised controlled trial* needed additional ‘rescue’ medication</td>
</tr>
<tr>
<td>• NSAIDs – all probably work</td>
</tr>
<tr>
<td>- COX-2 selective inhibitors (celecoxib) – use higher doses: 800mg then 400mg bid = indomethacin 50mg tid</td>
</tr>
<tr>
<td>• Steroids – use enough for long enough</td>
</tr>
<tr>
<td>- ~ 35mg prednisolone = indomethacin 50mg tid, naproxen 500mg bid</td>
</tr>
<tr>
<td>- intra-articular steroid</td>
</tr>
</tbody>
</table>


There is new evidence that shows that the microbiome influences inflammatory tone, increasing IL-1 release; new anti-IL-1 agents in development will seek to block this physiological pathway.

Conclusion

By seeking to achieve a cure for this chronic metabolic disease, we will reduce overall morbidity and may ensure benefit in respect of all-cause mortality associated with the common comorbidities of gout, such as hypertension, CKD, diabetes, CAD and chronic heart failure (Table 5).
Table 5: Summary – The gout picture

1. Gout is a curable chronic metabolic disease of urate deposition
   – Gout flares are symptoms

2. The lower the serum urate level, the faster the deposits are dissolved
   – Low serum urate (~<6.0mg/dl) must be maintained to prevent recurrence of flares
   – Option to ‘de-bulk’ specific urate deposits with ultra-low serum urate

3. Complex relationship between gout and many comorbidities

4. Anti-IL-1 therapy to treat acute flares is very effective and does not impact on the comorbidities of many gout patients

5. Inflammatory tone interacts with the SUA to initiate/influence flares

References


