An update on the management of gout
The management of gout involves treatment of an acute attack, lifestyle modification and urate lowering treatment to achieve a target serum urate level. Recent evidence shows that a starting dose of allopurinol based on eGFR provides a safe, practical and effective treatment regimen. Benzbromarone, a uricosuric medicine which is currently unapproved in New Zealand, is to become available, fully subsidised, under Special Authority criteria from 1 April, 2013. Although benzbromarone has been associated with rare cases of serious liver toxicity, there is evidence that supports its use as a further therapeutic option for patients if optimal use of allopurinol and/or probenecid has failed to achieve target urate levels or if these medicines are unable to be tolerated.

Genetics, lifestyle and co-morbidities influence the development of gout

Gout arises from the interaction of genetic and environmental factors, with diet and co-morbidities playing a significant role. It is more common in males and with increasing age. Co-morbidities such as obesity, type 2 diabetes, hypertension and chronic kidney disease that are associated with raised uric acid levels also contribute to an increasing prevalence of gout.1

The prevalence of gout in New Zealand, standardised for age, gender and ethnicity is approximately 4% in adults aged ≥ 20 years.2 However, gout is present in 11.7% and 13.5% of Māori and Pacific males, compared to 3.7% of European males, and 4% of Māori and Pacific females, compared to less than 1% of European females.2 Over one-third of Māori men and at least one-quarter of Pacific men aged over 65 years are affected by gout.2

Recent research has found that variants in specific genes are associated with a reduced ability for renal excretion of uric acid, and therefore increased risk of hyperuricaemia.3 A variant within the gene SLC2A9 increases the risk of gout by more than five times in Māori and Pacific peoples, and a variant within the ABCG2 gene increases the risk in European and Pacific peoples but not in Māori.3,4

The stages of gout

Asymptomatic hyperuricaemia is a common biochemical finding, with evidence of an association with hypertension, insulin resistance and diabetes, kidney disease and increased cardiovascular risk.6,7 Treatment of asymptomatic hyperuricaemia, is not currently recommended.2,4 While some

What is gout?

Gout is a common form of inflammatory arthritis caused by deposition of monosodium urate crystals in and around joints. Urate is formed by the metabolism of purines, both ingested and endogenous. Of the urate produced daily, the majority (approximately 70%) is excreted via the kidneys and the remainder is eliminated into the biliary tract. Hyperuricaemia is generally a result of either over-production or more frequently, renal under-excretion of urate, or both. Gout develops when the serum urate reaches super-saturation leading to precipitation and then deposition of monosodium urate crystals in joints and other sites, e.g. cutaneous tissues. Crystal release from deposits within a joint can cause an acute synovitis or lead to chronic inflammatory arthritis. Tophi develop from deposition in extra-articular sites if there is long-term hyperuricaemia. Kidney stones (most often due to calcium oxalate but also from deposition of urate crystals) may also develop within the collecting system of the kidney.

An acute attack of gout is extremely painful. Attacks are usually self-limiting, however, untreated or poorly treated gout can lead to chronic tophaceous gout, which may result in deformation and destruction of the joints, as well as urate nephropathy. Treating to achieve a target serum urate level of 0.36 mmol/L is associated with improved clinical outcomes for people with recurrent gout. A lower target of 0.30 mmol/L is recommended in some international guidelines for some people, such as those with extensive tophi.15
people with hyperuricaemia never develop acute symptomatic gout, the risk of developing gout increases as the urate level rises.

An acute attack of gout is characterised by the rapid onset of joint pain, associated with swelling and erythema due to the inflammatory response to the presence of urate crystals in the joint. Symptoms peak within 12 – 24 hours after the beginning of an attack. The majority of people will seek treatment due to pain, however, if untreated, most attacks will spontaneously resolve in seven to ten days. Some people will go on to have recurrent acute attacks with an asymptomatic period between attacks (referred to as intercritical gout).

N.B. Urate levels ideally should not be measured during an acute attack of gout, as they may be misleadingly normal during this time in 11 – 49% of people.

Chronic tophaceous gout may develop if recurrent gout remains untreated or incompletely managed with urate lowering treatment. This is characterised by the development of tophi (urate crystal deposition in soft tissue), more frequent acute attacks and an increase in the number of joints affected. There is a gradual worsening of inflammatory arthritis, erosive joint damage and, in some cases, urate nephropathy.

**General principles in the management of gout**

The management of gout can be split into three areas:

- Treatment of an acute attack
- Lifestyle modification
- Urate lowering treatment

**Treatment of an acute attack of gout**

For the majority of patients the first-line treatment in an acute attack of gout should be a non-steroidal anti-inflammatory drug (NSAID). A recommended regimen is naproxen 500 mg, repeated after 8 – 12 hours, then twice daily on the following day, tapering the dose as the attack resolves. Depending on individual patient circumstances, concurrent use of a proton pump inhibitor may be required.

Corticosteroids are an effective and often underused alternative treatment if the patient is unable to tolerate NSAIDs and infection has been excluded. A recommended regimen is oral prednisone 20 – 40 mg daily, gradually reduced over 10 – 14 days. Intra-articular injections of corticosteroid can be used if one or two joints are affected, e.g. trimcinolone acetonide (Kenacort-A), with the dose dependent on the size of the affected joint.

If a NSAID or corticosteroid is not appropriate, low dose colchicine may be used, and is most effective when started early in an attack (within 12 hours). The recommended initial dose for colchicine for the treatment of acute gout is 1 mg stat (two tablets). While some guidelines suggest that this is followed by 0.5 mg six hourly, up to a maximum dose of 2.5 mg per 24 hours on the first day and to a maximum of 1.5 mg on subsequent days, many patients will develop significant gastrointestinal toxicity with this dosing. A study comparing low dose (1.2 mg stat, followed by 0.6 mg one hour later) with high dose (1.2 mg stat, followed by 0.6 mg every hour for six hours) colchicine in the first 24 hours of acute gout showed no loss of efficacy but a significant reduction in adverse effects on the low dose regimen. The total dose of colchicine should not exceed 6 mg over four days (i.e. limit prescriptions to 12 tablets only) and a course of treatment with colchicine should not be repeated within three days.

The use of colchicine is “relatively contraindicated” in people with a creatinine clearance of < 60 mL/min. It should also be used with caution in older people, those with hepatic impairment or people who weigh < 50 kg. If used in these groups of patients the maximum dose in the first 24 hours should not exceed 1 mg and the total dose of colchicine should not exceed 3 mg over four days.

**Lifestyle modification**

People with gout or a history of gout should be encouraged to:

- Maintain an ideal weight
- Drink 2 L of water per day
- Exercise moderately, but during an acute attack; rest, elevate and cool affected joints
- Include low fat dairy, soy, vegetable sources of protein and foods high in vitamin C in their diet

People with gout or a history of gout should avoid:

- Dehydration
- Alcohol, particularly beer (if not avoided, then limit intake)
- Excess intake of foods rich in purines, e.g. red meat and offal (liver, kidneys), shellfish, oily fish, yeast extracts
- Soft drinks containing sucrose and fructose which interfere with tubular excretion of urate
Urate lowering treatment

Urate lowering treatment is beneficial in people who experience recurrent attacks of gout, e.g. two or more attacks in one year, and people who have tophi, renal impairment or changes characteristic of gout on x-ray. Urate lowering treatment should be initiated early before there has been any erosive damage to joints and ideally, before tophi have appeared. A review of the patient’s current medicines is recommended to re-assess the need for any medicines that may increase serum urate levels such as thiazide and loop diuretics.

Allopurinol is currently the most widely used medicine to reduce urate levels. It blocks the enzymatic conversion of hypoxanthine and xanthine to urate. It is recommended that allopurinol is initiated at least two weeks after an acute gout attack and used concurrently with either a low-dose NSAID (e.g. naproxen 250 mg, twice daily) or colchicine (0.5 mg, daily or twice daily) to prevent early gout flares. The optimal duration of anti-inflammatory prophylaxis after the initiation of urate lowering treatment has not been defined, however, it is commonly recommended for at least three – six months after achieving a serum urate level of ≤ 0.36 mmol/L.

Recent evidence has shown that a starting dose of allopurinol calculated at 1.5 mg per unit of eGFR, provides a safe, practical and effective treatment regimen. Although these doses may be lower than previously recommended, a “start low, go slow” approach is likely to reduce adverse effects, improve long term compliance and result in fewer attacks of acute gout during initiation of allopurinol.

Table 1 gives suggested starting doses for allopurinol, based on eGFR. The dose can then be slowly increased, e.g. by 50 mg increments per month, as guided by tolerance and the target serum urate level, to doses above 300 mg daily, even in patients with renal impairment. Higher doses of allopurinol, e.g. up to 600 mg daily, may be required in some patients to achieve target serum urate levels. Provided the starting dose is low (determined by eGFR) and the dose increments are made slowly, recent evidence has shown no increase in serious toxicity (specifically allopurinol hypersensitivity syndrome) with higher doses of allopurinol.

N.B. Allopurinol increases the toxicity of azathioprine when used concurrently, so the combination should be avoided because there is no reliable calculation to adjust the dose. Allopurinol may increase the plasma concentration of ciclosporin (cyclosporin).

Patients who are intolerant of allopurinol may require treatment with a uricosuric medicine such as probenecid or benzbromarone (over page). Combination treatment with allopurinol and probenecid may be helpful to achieve target urate levels in some patients.

Probenecid should be initiated at a dose of 250 mg, twice daily, for one to two weeks, then increased to 500 mg, twice daily, for one to two weeks, and then increased (by 500 mg daily, each week) to a maximum of 2000 mg, daily, in divided doses. Patients should be advised to maintain an adequate fluid intake to prevent the formation of uric acid stones. Probenecid, like other urate lowering medicines, should not be initiated during an acute attack of gout, but if the patient is already established on a stable dose then it may be continued. The efficacy of probenecid is significantly reduced in patients with eGFR < 50 mL/min/1.73m², and it should be avoided in patients with a history of kidney stones.

Febuxostat, a novel xanthine oxidase inhibitor, is available in other countries and there is some evidence that it may be more effective than allopurinol (300 mg) in achieving target urate levels in patients with renal impairment. Pegloticase, a recombinant uricase administered intravenously, may have a role for a limited number of patients with severe refractory tophaceous gout, but is also not currently available in New Zealand.

Table 1: Suggested starting doses of allopurinol

<table>
<thead>
<tr>
<th>eGFR mL/minute/1.73 m²</th>
<th>Starting dose allopurinol</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>50 mg, weekly</td>
</tr>
<tr>
<td>5 – 15</td>
<td>50 mg, twice weekly</td>
</tr>
<tr>
<td>16 – 30</td>
<td>50 mg, every two days</td>
</tr>
<tr>
<td>31 – 45</td>
<td>50 mg, daily</td>
</tr>
<tr>
<td>46 – 60</td>
<td>50 mg and 100 mg, alternate days</td>
</tr>
<tr>
<td>61 – 90</td>
<td>100 mg, daily</td>
</tr>
<tr>
<td>91 – 130</td>
<td>150 mg, daily</td>
</tr>
<tr>
<td>&gt;130</td>
<td>200 mg, daily</td>
</tr>
</tbody>
</table>

* Based on 1.5 mg allopurinol per unit eGFR.
The role of benzbromarone in the management of gout

Benzbromarone is a uricosuric medicine that increases the net renal excretion rate of urate. Benzbromarone inhibits the action of urate transporters in the renal tubules such as SLC2A9, URAT1 and ABCG2, leading to increased renal excretion of urate. Probenecid acts on other urate transporters, but does not inhibit SLC2A9.3 There is some evidence that benzbromarone, therefore, may be of particular clinical benefit in populations who have the genetic variant of SLC2A9 that increases risk of hyperuricaemia, e.g. Māori and Pacific peoples, however, this is an ongoing area of research.3, 4

It is recommended that discussion with, or referral to a Rheumatologist, should occur if treatment with benzbromarone is being considered for a patient with gout. A trial of benzbromarone may be an appropriate choice if:

- Optimal use of allopurinol (e.g. up to 600 mg/day) has failed to achieve a serum urate concentration of ≤ 0.36 mmol/L or there are intolerable adverse effects
- The addition of probenecid (e.g. up to 2 g/day) has failed to achieve a serum urate concentration of ≤ 0.36 mmol/L or there are intolerable adverse effects, or probenecid is contraindicated due to renal impairment
- The patient meets the Special Authority criteria (see “Benzbromarone to be subsidised for the treatment of gout”)

People who have large tophaceous deposits and people taking furosemide, who usually require larger doses of allopurinol (relative to their renal function) to achieve target serum urate levels, are likely to make up a significant portion of this group of “difficult to treat patients”, for whom benzbromarone may be considered.14, 18 Benzbromarone can be used in patients with moderate renal impairment.10

Recommended dosing of benzbromarone

Benzbromarone is usually started at a low dose, e.g. 25 – 50 mg daily, and then gradually increased, as required, guided by target serum urate levels.19 Although the maintenance daily dose for benzbromarone can range from 50 mg – 200 mg,10 in practice it is usually prescribed in a single maximum daily dose of 100 mg to avoid hepatic adverse effects, which are more likely at higher doses. Target serum urate levels can be achieved in the majority of patients with a dose of 100 mg benzbromarone.

Benzbromarone is not recommended for use in people with an eGFR < 20 mL/min/1.73m², but can be used in people with moderate renal impairment as it is predominately metabolised by the liver.19

Benzbromarone, like other urate lowering medicines, should not be initiated during an acute attack of gout, however, if patients are already established on any urate lowering medicine, including benzbromarone, then it is usual practice to continue the treatment during an acute attack.

Adverse effects with benzbromarone

Benzbromarone has been in clinical use for over thirty years and appears to be generally well-tolerated with few adverse effects, however, it has been associated rarely with fulminant hepatic hepatitis and liver failure.19 Reports of serious liver toxicity (including one death) led to removal of the medicine from the European market in 2003. The incidence of serious adverse effects such as liver toxicity is unknown, because the reporting and recording of all adverse effects is limited due to its unapproved status in New Zealand, and the low level of world-wide use.

Under the Special Authority criteria, patients taking benzbromarone should have regular liver function tests (LFT) to monitor for any change in liver function. For the first six months LFTs should be requested at least monthly and thereafter at least three monthly. However, the optimal frequency of testing required varies in the literature because the rate of development of hepatitis is unknown.

A more cautious approach, although potentially difficult in terms of patient adherence, is to measure LFTs:19

- At baseline
- Weekly for one month
- Fortnightly for the second month
- Monthly for three – six months
- Two monthly thereafter

Precautions

Benzbromarone should not be used in people with known hepatic disease, and should be used with caution in people with a history of hepatic impairment or people who are also taking other medicines which may be potentially hepatotoxic. People who have an excess intake of alcohol are also likely to be more at risk of liver toxicity.
Patients taking benzbromarone should be advised to drink adequate fluids (2 – 4 L/day) due to the risk of nephrolithiasis (kidney stones) which can occur with any uricosuric medicine. Benzbromarone should not be used in people with a past history of kidney stones.

Benzbromarone is currently an unapproved medicine in New Zealand, although it has been available under Section 29 on a named patient basis for several years. From 1 April, 2013, a 100 mg tablet will be available, fully subsidised, on the Pharmaceutical Schedule for patients who meet the Special Authority criteria. Although not a requirement, it is recommended that patients who may benefit from benzbromarone, and who meet the criteria for subsidy, should be referred to a Rheumatologist (or discussed with a Rheumatologist).

The Special Authority criteria for six months approval are as follows;

1. Any of:
   1.1 The patient has a serum urate level greater than 0.36 mmol/L despite treatment with allopurinol at doses of at least 600 mg/day and appropriate doses of probenecid; or
   1.2 The patient has experienced intolerable side effects from allopurinol such that treatment discontinuation is required and serum urate remains greater than 0.36 mmol/L despite appropriate doses of probenecid; or
   1.3 Both:
      1.3.1 The patient has renal impairment and serum urate remains greater than 0.36 mmol/L despite optimal treatment* with allopurinol; and
      1.3.2 The patient has a rate of creatinine clearance greater than or equal to 20 mL/min; or

2. The patient is receiving monthly liver function tests.

Renewal of the Special Authority is valid for two years provided that:

1. The treatment remains appropriate and the patient is benefiting from treatment; and
2. There is no evidence of liver toxicity and patient is continuing to receive regular liver function tests (at least every three months)

* Optimal treatment with allopurinol in patients with renal impairment is defined as treatment to the creatinine clearance-adjusted dose of allopurinol then, if serum urate remains greater than 0.36 mmol/L, a gradual increase of the dose of allopurinol to 600 mg daily or the maximum tolerated dose.

** Renal impairment is not necessarily a contraindication to the use of allopurinol

For full details, see the Pharmaceutical Schedule, available from: www.pharmac.health.nz

Benzbromarone is an inhibitor of the cytochrome P450 isoenzyme CYP2C9 which is required for the metabolism of some medicines, e.g. warfarin, and therefore it may increase the anticoagulant effect of warfarin. The effect of benzbromarone may be antagonised by aspirin and other salicylates.
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Key dates for changes to diabetes management products

- 1 September 2012 – CareSens range of blood glucose meters and testing strips listed on the Pharmaceutical Schedule
- 1 December 2012 – CareSens range of blood glucose meters now the only meters subsidised
- 1 March 2013 – only CareSens range of testing strips will be subsidised

Contact information

Free phone help line for health professionals and to order sample meters – 0508 CARESENS (0508 2273 7367)
Free phone help line for patients – 0800 GLUCOSE (0800 458 2673)
CareSens information online – www.caresens.co.nz
Details of funding changes, seminars and general information – www.pharmac.govt.nz

See www.bpac.org.nz for a full version of this information sheet
The Common Form module combines features from the Diabetes and CVD Management modules to produce a streamlined, standardised tool that assists in clinical review, disease monitoring and clinical management.

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