New urate-lowering therapies in Aotearoa New Zealand: a response to Dr Lance Gravatt's letter on benzbromarone hepatotoxicity

Gout is now the most common form of inflammatory arthritis in Aotearoa New Zealand, affecting 3.2% of New Zealand European, 6.1% of Māori and 7.6% of Pacific adults. Inadequately treated gout results in joint damage, ulceration and permanent disability. Māori and Pacific people have particularly high rates of severe gout, causing joint pain, accelerated joint damage and work disability.

Given the major impact of this disease in our community, the Māori Gout Action Group and the New Zealand Rheumatology Association welcome both the recent PHARMAC funding of benzbromarone through Special Authority and Medsafe approval of febuxostat.

The key strategy for preventing gout attacks, tophi and joint damage in patients with gout is long-term urate-lowering therapy to reduce the serum urate below 0.36 mmol/L, which leads to dissolution of MSU crystals within the joints. Allopurinol is first-line treatment for urate-lowering therapy, although is often used at inadequate doses within our community.

Benzbromarone is a potent uricosuric agent that has documented efficacy in patients with gout. It is particularly beneficial for patients with renal impairment who are intolerant to allopurinol or have an insufficient response to recommended doses of allopurinol.

Benzbromarone was widely used in Europe until 2003 when Sanofi-Synthelabo withdrew the drug after reports of fulminant hepatitis leading to death in two patients. Benzbromarone remains available in Japan, Brazil and certain European countries, such as Spain, Germany, and Austria. This complication is extremely rare and is likely to be prevented by regular monitoring of liver function tests in patients receiving this drug.

A number of experts have questioned the rationale for withdrawal of benzbromarone based on a risk-benefit analysis. Randomised controlled trials published in the last 5 years have demonstrated the superior efficacy of benzbromarone over probenecid in patients who have failed allopurinol treatment (due to inadequate serum urate lowering or intolerance), and that benzbromarone has superior efficacy compared with allopurinol 300mg daily.

In these studies, benzbromarone was well tolerated with no reports of hepatotoxicity. Observational studies have also indicated that benzbromarone is effective and well tolerated. The gout treatment guidelines for the European League Against Rheumatism (EULAR) have recommended that benzbromarone can be considered in patients with renal impairment.

Regular monitoring of liver function tests and serum urate is essential to monitor drug safety and efficacy. Benzbromarone may interact with warfarin to increase the
anticoagulant effect and close monitoring of the INR is needed if these drugs are co-prescribed.\textsuperscript{7} Benzbromarone should also be avoided in people with previous nephrolithiasis. Although now funded on Special Authority for people with gout who have failed treatment with allopurinol and probenecid, benzbromarone remains accessed through Section 29 of the Medicines Act.

Recent results from the ‘Genetics of Gout in Aotearoa’ study provide further rationale for use of benzbromarone for those New Zealanders who are most severely affected by gout. Genetic variations in a particular renal urate transporter gene \textit{SLC2A9} are extremely common in Māori and Pacific people with gout and strongly increase the risk of gout in these groups.\textsuperscript{8}

Unlike other available urate-lowering therapies, benzbromarone specifically inhibits this transporter. Furthermore, genetic variants in \textit{CYP2C9} that might predict poor metabolism of benzbromarone and higher risk of hepatotoxicity are very rare in Māori and Pacific people with gout.\textsuperscript{9} Our clinical experience in the last 10 years is that benzbromarone is well tolerated and highly effective in those who managed to access this drug (through hospital exceptional circumstances or charitable donation schemes).

Febuxostat is also a potent urate-lowering agent, with greater efficacy than fixed dose allopurinol (300mg daily for those with normal renal function).\textsuperscript{10} This agent has recently been approved by Medsafe for use in New Zealand but is not currently funded by PHARMAC.

In the phase 3 studies of febuxostat, abnormal liver function tests were observed in 4–5% of participants, leading to withdrawal of febuxostat in 1–2% of participants. Liver function test monitoring is also recommended when prescribing this agent.

Febuxostat is a xanthine oxidase inhibitor, and therefore co-prescription with azathioprine should be avoided due to the potential for bone marrow suppression. This drug-drug interaction is of clinical importance, given the severe gout that frequently occurs in solid organ transplant recipients.

Increased access to these urate-lowering agents offers great promise for improved management of gout within our community, particularly for those patients who are intolerant to allopurinol or when adequate dosing of allopurinol does not lead to serum urate targets.

We hope that the availability of these agents will also promote greater general awareness of the importance of long-term urate-lowering therapy for gout prevention, in the first instance allopurinol at doses sufficient to reduce serum urate concentrations (see \url{http://www.healthpointpathways.co.nz/gout-prevention}).

Central to effective management of gout, irrespective of the drug used, is patient education about medications and potential side effects, consideration of drug interactions, and monitoring of efficacy and toxicity.

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References:


