# Why better treatment of gout is needed

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**ABSTRACT**

*The treatment of gout is thought to be simple, but in reality we are confronted regularly with patients who do not adhere to treatment and patients who have other medical conditions that render the choice of therapy difficult. A treat-to-target approach is essential in order to manage hyperuricaemia effectively and this, combined with a better use of existing treatments, offers the best way forward.*

## Introduction

Gout is a urate deposition disease that results from prolonged hyperuricaemia and manifests typically as recurrent acute attacks of monoarthritis. The causes of hyperuricaemia and gout are now well established, and effective treatments have been discovered. Over the last fifty years, our medical interest in the disease has gradually diminished, in the mistaken belief that the "problem has been solved". However, the reality is far from this. Gout is the most common form of inflammatory arthritis, its worldwide prevalence continues to increase, and many patients still suffer from severe and crippling gout. Part of the explanation lies in the epidemiology, for the incidence of gout and hyperuricaemia increases with age and in particular in males (1); with an ageing population, there are simply more patients affected. Secondly, the aged patient tends to have more comorbid disease that makes effective treatment more complicated.

## What are the objectives of treatment?

The treatment is based on a two-pronged approach - firstly to alleviate pain and inflammation of an acute attack and secondly to correct the underlying metabolic abnormality - hyperuricaemia (Table I). Unfortunately, doctors and patients often focus their attention only on the acute attack, and forget to address hyperuricaemia, the cause of the problem. We have effective drugs to treat the acute attack, but the challenge we frequently face is to choose a treatment that is effective for alleviating pain and inflammation, but which does not provoke iatrogenic side effects in elderly patients who have many other significant medical problems. NSAIDs have clear limitations in patients with renal and cardiovascular diseases, and colchicine is not always well tolerated, even at the lower dose that is currently recommended. Recent studies have shown that a short course of oral steroids for up to 5 days is as effective as full dose NSAID therapy in terms of pain relief (2). Studies have also demonstrated that IL-1 inhibitors can be effective in an acute attack, but their place in the therapeutic strategy of acute gout is not yet clearly established (3).

Most patients with gout require urate-lowering therapy (ULT), as dietary and lifestyle measures alone are unlikely to be sufficient to control hyperuricaemia. As the solubility limit of MSU in plasma is around 6mg/dL (≈360umol/L), the aim of ULT is to bring the urate level to below this point, in order to prevent new crystal formation and accelerate crystal dissolution. In ULT trials that have assessed tophus size, dramatic changes have been seen when urate levels have been lowered by pegloticase (4). It is therefore important that when ULT is prescribed, the physician checks that the level of uric acid (UA), and adjusts treatment to achieve the minimum target level of 6mg/dL. This treat to target approach has now gained general acceptance in rheumatology, but in the treatment of gout, has only been applied recently.

The ACR has recently published their guidelines on the management of gout (5, 6) and an updated set of EULAR guidelines will be published shortly.

## Why is gout so poorly treated?

Many different studies have documented that gout is badly treated, and poorly

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treated gout is associated with worse outcomes. The adherence to prescribed ULT is poor, with more than half the patients stopping therapy within 12 months. Furthermore, patients who are on ULT are often not treated to the UA target (see above). Many factors, ranging from physician education to cultural stereotypes that stigmatise gout, have been put forward as explanations (7), but the clinically relevant question is how to address these barriers and to improve patient adherence. A pilot study targeting patient education in gout has shown that dedicated patient education combined with regular monitoring of UA levels can improve compliance and 90% of patients achieved the target UA level (8). The challenge is to implement such programs in primary care, where the bulk of gout patients are seen.

**Table I.**

| Basis of gout therapy | |
|---|---|
| Managing the acute attack of gout | Managing hyperuricaemia |
| • Effective treatment of inflammation | • Dietary modification |
| • Reduction of pain | • ULT |
| • Avoid iatrogenic complications | • Use of prophylaxis to prevent gout flare during ULT |
| | • Patient education and adherence to treatment |

## Using old drugs better

Although there are a small number of patients who do not respond to the available treatments or who do not tolerate them, the majority does respond adequately. Among the available ULTs, allopurinol is the most commonly used, but in clinical practice, it is often under dosed, leading to UA levels that are above the treatment target. In the pivotal clinical trials of febuxostat, the standard 300mg dose of allopurinol was used as a comparator and approximately 60% of patients on this dose did not reach target UA level (9). These findings have been reproduced in other clinical trials of other ULTs. The conclusion is that in most patients, 300mg allopurinol is not sufficient, and the dose should be gradually escalated in order to achieve target UA levels.

Fears that dose escalation may provoke side effects; in particular the potentially lethal allopurinol hypersensitivity syndrome (AHS) has been a major factor influencing prescribing practice. These reactions typically occur early on during therapy, and the risk may be increased in patients with chronic renal impairment. In small-scale studies however, Stamp and colleagues have shown that even in the setting of chronic renal disease, slow dose escalation of allopurinol was safe and helped to achieve the UA target (10). Concerns about AHS are justified, in particular in Asian patients where the occurrence of AHS is linked to the presence of the HLAB*5801 allele, and testing for this gene may be justified in high risk populations (5), but probably not in the Caucasian population.

In most cases, ULT is prescribed as monotherapy. However, in patients who do not achieve the UA target on monotherapy, the combination of a xanthine oxidase inhibitor and a uricosuric has been suggested (5). This approach has not been proven in the randomised clinical trial setting, but empirical experience has confirmed its utility.

## New drugs

Although gout is a very common disease and hyperuricaemia is a condition that has been implicated in the pathogenesis of chronic kidney disease, hypertension and cardiovascular disease, there have been surprisingly few novel drugs introduced. Allopurinol was developed in the 1950s, and for 50 years was the only xanthine oxidase inhibitor in clinical use. With the introduction of febuxostat, there has been renewed interest in gout therapy. However, when compared to the number of drugs that have been developed for treating hypercholesterolaemia or hypertension, gout and hyperuricaemia lag far behind in terms of therapeutic choice. The advantages of febuxostat over allopurinol include its effectiveness in patients with chronic renal disease (11) and the absence of severe cutaneous side effects in patients who did not tolerate allopurinol (12, 13). Another xanthine oxidase inhibitor, topiroxostat has recently been introduced in Japan (14), but it has not yet gained a world-wide market.

As renal excretion accounts for over 80% of the daily elimination of UA, uricosurics are potentially an important option. Current uricosurics are probenicid and benzbromarone, but the latter drug has a very limited availability because of concerns over hepatotoxicity. Lesinurad, a new uricosuric that acts via inhibition of the urate transporter SLC22A12 (URAT 1), has been studied in combination with allopurinol and demonstrated urate lowering efficacy (15). It has recently been approved by the FDA to treat gout.

## Future challenges

*Hyperuricaemia*

As mentioned earlier, epidemiological studies have implied that hyperuricaemia (without clinical gout) could have a deleterious role in the pathogenesis of cardiovascular and chronic kidney disease. A possible underlying mechanism that explains these findings is the enzyme xanthine oxidase, which is capable of generating reactive oxygen species as well as uric acid as reaction products. Xanthine oxidase inhibition has been shown in a number of experimental settings to have beneficial effects, but in man, we lack sufficient evidence to recommend treatment of asymptomatic hyperuricaemia in the absence of clinical gout. The exception is in Japan, where hyperuricaemia in the context of pre-existing cardio renal disease, is treated with ULT (16). Future research and large clinical trials are needed to study the costs and benefits of treating hyperuricaemia.

*Treating from the first attack*

Current recommendations on gout are vague about the need to treat gout after the first attack, and this attitude is partly based on the perceived risk of drug-induced side effects. This attitude may need to be revised in light of results from imaging studies using ultrasound

and dual energy CT (DECT), which demonstrated that gout deposits are detectable at early stages of the disease and even in asymptomatic hyperuricemic subjects. The more widespread use of these imaging modalities is likely to change our treatment strategy, as starting ULT early when the total burden of UA deposit is small may be more effective in obtaining a "cure" than when UA deposits are more abundant. Again, there have been no clinical trials that have addressed this problem.

*Developing new drugs*

As alluded to earlier, new drugs are still scarce in the gout field and it would be of great clinical benefit that the clinician has a range of treatment options when confronted with patients who cannot tolerate one or another treatment. The recent genetic studies on gout and hyperuricaemia have identified associations with multiple loci, some related to the renal handling of urate and others that are linked to hepatic carbohydrate metabolism (17). These findings provide potential new targets for drug development.

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