Student: Amy Thomas
Title: Systematic literature review of the effects of urate lowering on clinical outcomes in gout
Supervisors: Professor Lisa Stamp and Associate Professor Will Taylor
Sponsor: Arthritis NZ

Introduction:
Gout is a common form of arthritis which most often affects men, with particularly high rates in Maori and Pacific Island people. It involves extremely painful recurring attacks of joint tenderness and swelling which can lead to joint damage and collections of urate crystals under the skin (tophi) in the longer term. Gout is caused by the deposition of monosodium urate crystals within the joints and surrounding tissues as a result of high concentrations of uric acid in the blood. These crystals set off an inflammatory response which results in a gout attack. Treatment revolves around decreasing and maintaining low blood uric acid levels over time, with a target serum urate of < 6mg/dl as at this concentration further crystals cannot form and those present can dissolve.

While there are medications that are effective at decreasing blood uric acid it has not yet been shown that this reduction results in an improvement in outcomes that are important to patients, such as the number of gout flares, physical functioning and tophi resolution. This is key as improving people's quality of life is the major reason for treatment. An association with clinical outcomes is also the final requirement for uric acid to be validated as a biomarker by an international body called OMERACT.

A biomarker is a characteristic that can be measured as an indicator of biological processes, and as such can be used to evaluate the presence or progression of disease. The benefit of biomarkers is that they can be used by clinicians and patients as an aid in decision making regarding disease activity and treatment efficacy. However their use depends on the quality of the data that supports their application in clinical practice. Previous research has shown that blood uric acid fulfils all of the other OMERACT criteria for a biomarker, and so the last component is investigating its link with clinical outcomes.

Aim:
The aim of this study is to undertake a systematic literature review of the existing data available regarding the association between a reduction in blood uric acid and an improvement in outcomes important to gout patients. This will provide evidence supporting the validation of blood uric acid as a biomarker, which would make it the first accepted biomarker in the field of rheumatology.

Method:
A systematic literature review was done in order to search for the studies currently available in regard to this topic. A literature review involves using a structured approach to identify, analyse and summarise all of the evidence relating to a particular question. A variety of different statistical methods can then be used to synthesise these study findings. For this review the papers of interest were randomised controlled clinical trials (RCTs) of adults with gout on urate-lowering medication which measured at least one patient-relevant outcome and were of duration of 3 months or more.

Five major electronic databases, paper references and abstracts of rheumatology conferences were searched up to November 2014. Searches involved using the term "gout" in conjunction with "uric acid" or "serum urate", various medications, or clinical outcomes such as gout

flares, tophi and quality of life. The papers were assessed for suitability, and data from the selected studies was then extracted using a pre-formed spreadsheet.

Results:
In total 1,538 unique papers were identified, of which 1,351 were excluded as irrelevant by title. 187 abstracts were reviewed, resulting in the assessment of 66 full papers for their suitability. The review considered factors such as study design, data available and outcomes measured. 13 papers which fulfilled the requirements were selected, covering a total of 11 studies. These studies were RCTs and their extensions, with durations between 3 months and 5 years and involving multiple different urate-lowering medications.

Although statistical analysis had not been finished by the completion of this studentship preliminary descriptive analysis suggests that there is an association between blood uric acid levels and various patient-centred outcomes. There is currently limited RCT data on clinical outcomes in gout; however there is more extensive evidence from observational trials.

Some RCTs, particularly those of shorter duration, were not able to find significant differences in gout flares and tophi resolution across treatment groups which achieved varying blood uric acid levels. The authors suggested additional longer studies were required as it takes several months for medication effects to become apparent and the data was becoming more convincing towards the ends of the trials. One study demonstrated that patients treated with urate-lowering medication did experience a decreased number of flares and tender joints as well as a greater likelihood of tophi regression. These participants also reported a meaningful improvement in their pain levels and quality of life. The longer extension studies were able to show an association between a lowered blood uric acid and better patient-relevant outcomes. Patients who responded to treatment and were able to maintain blood uric acid within the target range (< 6mg/dl) showed continued improvement over time with significantly lower flare rates and greater tophi reduction and resolution.

These clinical trial findings are supported by observational studies which track people over time. It has been demonstrated that the speed of tophi reduction is inversely proportional to the blood uric acid concentration, meaning the lower the uric acid level achieved the faster the tophi resolution. Other large studies have shown that patients achieving the target blood uric acid level of < 6mg/dl were significantly less likely to have gout flares. In turn, the number of flares and presence of tophi is associated with quality of life and physical function, which provides the link between blood uric acid and patient experience.

Conclusion:
This systematic review found only a moderate amount of research regarding the relationship between blood uric acid and clinical outcomes such as flare and tophi resolution in people with gout. Statistical analysis is pending, however the available evidence indicates that there is an association between a reduction in blood uric acid and an improvement in patient-centred outcomes. The RCT and extension findings are supported by observational data and what is already known about the role of uric acid in gout. By confirming the link between uric acid and clinical outcomes the requirements for serum urate to be validated as a biomarker can be met, and hopefully this will be verified by OMERACT in 2016. The use of blood uric acid levels may be able to further improve the treatment of patients with gout, as clinicians could estimate the potential benefit of a certain decrease in urate. This could also pave the way for the validation of other biomarkers in the future, with the aim of providing the best patient care.