

Predictors of Success in Gout Treatment

In this issue of *The Journal*, Singh, *et al*, from the University of Alabama, asked the key question regarding outcomes for people with gout: what are the factors associated with achieving and maintaining target serum urate (SU) concentrations with allopurinol¹? To examine this, they have accessed a large, longitudinal cohort of patients with gout in the US Veterans Administration (VA) system from 2002 to 2012.

To be included in the study, a patient needed a diagnostic code of gout for ≥ 1 inpatient episode or ≥ 2 outpatient visits, a new prescription for allopurinol, and a record in the VA system for at least 12 months. A successful outcome was achieving a target SU concentration of < 6 mg/dl (0.36 mmol/l) 14 days or more after the index allopurinol treatment. Successful maintenance was defined as those whose SU remained < 6 mg/dl at all subsequent measurements.

There were 627,693 patients with gout in the VA system and 198,839 patients had a new prescription of allopurinol. However, only 41,153 had at least 1 SU result recorded and only 42% of these reached the target SU. This took a mean of 9 months to achieve. Only 17,402 incident allopurinol users had 2 or more SU results and of these, 42% achieved and maintained SU < 6 mg/dl for all blood samples tested over the period of observation. These findings are not surprising from what we know about outcomes for people with gout. However, they are depressing given that this form of arthritis can be controlled very well, if managed appropriately, in almost all cases.

The need to effectively manage gout is increasingly recognized as important because (1) gout is prevalent, and increasingly so, despite the proven effectiveness of urate-lowering therapies (ULT) such as allopurinol^{2,3,4}; (2) the effect on individuals, their families, and society has been significantly underappreciated^{5,6}; and (3) the documented poor adherence to ULT ($< 50\%$)⁷ has been moderately resistant to a wide range of interventions^{8,9,10,11}. Further, there is increasing concern that poorly controlled gout is a harbinger of premature and serious cardiovascular and/or renal impairments^{9,12}.

A significant proportion of people with gout do not seek medical care at all, accepting the condition as an inevitability that has to be endured. This is more likely in communities where the condition is very prevalent, and more severe, such

as some Māori and Pacific Islander communities¹³. Further, a significant number of people who start ULT for recurrent attacks abandon therapy altogether¹⁴. This is commonly because acute attacks of gout continue or even increase for a period of time when ULT is begun, a disappointment for those unaware that this might happen. Without sufficient forewarning and advice about the best course of action if an acute attack does occur during establishment of ULT, it is perhaps not surprising that people are so discouraged that they cease their therapy. Starting with a low dose, commonly 100 mg/day of allopurinol, and increasing the dose after 2 to 5 weeks is recommended (only if the target urate concentration has not been reached)¹⁵. Also, concomitant prophylaxis, most commonly colchicine or nonsteroidal antiinflammatory drugs, is advised for the first 6 months of ULT¹⁶. It is also well known that stopping and/or re-starting ULT, through forgetting to take doses, increases the risk for an acute attack – again a disincentive to ongoing adherence. This is quite complex information for the doctor to convey and the patient to absorb and comprehend during a short consultation. Lack of patient knowledge is considered a significant factor contributing to the very poor adherence⁶. This may, in part, explain why adherence to ULT is worse than in cases of other conditions that require chronic medication such as heart failure or diabetes¹⁷.

To date, knowledge of factors that affect the likelihood of success in achieving and maintaining SU ≤ 6 mg/dl, and thus control of gout attacks, has focused on short-term achievement of target SU and demographic and clinical characteristics of the patients. There has been less attention paid to healthcare systems and factors affecting access to healthcare. Singh, *et al* hypothesized¹ that applying Andersen's Behavioral Model would usefully broaden our understanding of enabling and predisposing factors influential in achieving and maintaining target SU, because the model incorporates societal and healthcare system factors¹⁸.

VA Informatics and Computing Infrastructure (VINCI) was instrumental in accessing multiple relevant VA databases and allowing data linkage for individual members of the cohort. Multivariable analyses revealed that success in achieving target SU was significantly associated with older age, male sex, having a rheumatologist as the main provider

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of gout care, smaller bed-size hospitals, and a Midwest US location of the healthcare facility. Lower likelihood of achieving target was associated with higher SU pre-commencement of allopurinol dosing [> 8 mg/dl (0.48 mmol/l)] and longer duration of gout.

Importantly and somewhat unusually, Singh, *et al* looked at the odds predicting success in maintaining SU below the target over time¹. These factors were similar to those predicting achievement of target SU after commencing therapy. Associated with significantly lower odds of maintaining target SU were heart disease, mild liver disease, diabetes, renal disease, malignancy, being single, a southern US rather than midwestern location, and an index SU > 8 mg/dl prior to the first dose of allopurinol. Broadly speaking, it seemed comorbidities were associated with a lower likelihood of both achieving and maintaining SU target concentration, a finding at odds with the discoveries of some other studies¹⁹.

Additional multivariable and exploratory analyses looked at previous allopurinol use, allopurinol initial and end doses, rates of escalation of dose, and medication possession ratios. Associations with success in achieving target SU were higher starting and maintenance doses, dose escalation *per se*, and higher medication possession ratios, the latter an index of adherence.

What can we learn from this analysis of stimulants and impediments to achieving and maintaining SU targets in this large, multicenter, multijurisdictional, incident allopurinol user cohort of patients with gout? Ease of physical access of our patients to good-quality care and rheumatologist involvement emerged as key predictors of success. Because most gout is managed in primary care in developed countries and rheumatologist involvement is minimal (in Singh, *et al*'s study, fewer than 3% of patients had rheumatologist care¹), an attractive option is to use technology such as telehealth and mobile apps to link management expertise with patients wherever they are²⁰.

Doherty, *et al*²¹ have shown outstanding effect on attainment and maintenance of target SU of close supervision of patients with gout receiving ULT by trained nurses, but resourcing this approach on a large scale is challenging. Pharmacists, who are often well-placed to monitor medication adherence, offer a potentially cost-effective approach to improving outcomes for patients^{22,23}.

Once a knowledgeable healthcare professional, be it primary care physician, rheumatologist, nurse, or pharmacist, is overseeing the education, monitoring, and ULT dose optimization of individual patients, then the currently unacceptable rates of adherence to ULT, and thus failed prevention of gout, will be overcome. It seems that a large proportion of patients need close supervision for some time if they are to join the ranks of those who will remain adherent to ULT and be relieved of repeated gout attacks. Singh, *et al*'s work importantly indicates that we need also to individualize

management according to the health system in which our patients are located because this affects the likelihood of a patient's access to the care most likely to be successful¹. It also shows the power of longitudinal tracking of patients and linking relevant large data sources to identify and focus on those patients who are slipping through the cracks.

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