Editorial

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 allopurinol[1]? 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 communities[13]. Further, a significant number of people who start ULT for recurrent attacks abandon therapy altogether[14]. 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 ULT[16]. 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 adherence[6]. 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 diabetes[17].

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* hypothesized[1] 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 factors[18].

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

See Effectiveness of allopurinol in gout, *page 449*

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 time[1]. 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 studies[19].

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 care[1]), an attractive option is to use technology such as telehealth and mobile apps to link management expertise with patients wherever they are[20].

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 successful[1]. 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.

RICHARD OSBORNE DAY, MD,
Professor of Clinical Pharmacology,
St. Vincent's Hospital, and
University of New South Wales;
MATHEW JAMES COLESHILL, PhD,
Postdoctoral Research Fellow,
St. Vincent's Clinical School,
University of New South Wales;
SOPHIE LENA STOCKER, PhD,
Senior Hospital Scientist,
St. Vincent's Hospital,
and Senior Lecturer,
St. Vincent's Clinical School,
University of New South Wales;
AMY DANH NGUYEN, PhD,
Postdoctoral Research Fellow,
Centre for Health Systems and
Safety Research,
Australian Institute of Health Innovation,
Macquarie University,
and St. Vincent's Clinical School,
University of New South Wales, Sydney;
PHILIP ROBINSON, PhD,
Associate Professor,
Royal Brisbane Hospital,
and the University of Queensland,
Brisbane;
EINDRA AUNG, PhD,
Postdoctoral Research Fellow,
St. Vincent's Clinical School,
University of New South Wales,
Sydney, Australia.

Address correspondence to Dr. R.O. Day, Department of Clinical Pharmacology and Toxicology, St. Vincent's Hospital, Darlinghurst, Sydney 2010, Australia. E-mail: r.day@unsw.edu.au

REFERENCES

1. Singh JA, Yang S, Saag KG. Factors influencing the effectiveness of allopurinol in achieving and sustaining target serum urate in a US Veterans Administration gout cohort. J Rheumatol 2020;47:449-60.
2. Pisaniello HL, Lester S, Gonzalez-Chica D, Stocks N, Longo M, Sharplin G, et al. Gout prevalence and predictors of urate-lowering therapy use: results from a population-based study. Arthritis Res Ther 2018;20:143.
3. Rai SK, Avina-Zubieta JA, McCormick N, De Vera MA, Shojania K, Sayre EC. The rising prevalence and incidence of gout in British Columbia, Canada: population-based trends from 2000 to 2012. Semin Arthritis Rheum 2017;46:451-6.
4. Bardin T, Bouee S, Clerson P, Chales G, Flipo R, Liote F, et al. Prevalence of gout in the adult population of France. Arthritis Care Res 2016;68:261-6.
5. Singh JA. The impact of gout on patient's lives: a study of African-American and Caucasian men and women with gout. Arthritis Res Ther 2014;16:R132.
6. Vaccher S, Kannangara DR, Baysari MT, Reath J, Zwar N, Williams

KM, et al. Barriers to care in gout: from prescriber to patient. J Rheumatol 2016;43:144-9.
7. Yin R, Li L, Zhang G, Reath J, Zwar N, Williams K, et al. Rate of adherence to urate-lowering therapy among patients with gout: a systematic review and meta-analysis. BMJ Open 2018;8:e017542.
8. Ramsubeik K, Ramrattan LA, Kaeley GS, Singh JA. Effectiveness of healthcare educational and behavioral interventions to improve gout outcomes: a systematic review and meta-analysis. Ther Adv Musculoskelet Dis 2018;10:235-52.
9. Gonzalez-Senac NM, Bailen R, Torres RJ, de Miguel E, Puig JG. Metabolic syndrome in primary gout. Nucleosides Nucleotides Nucleic Acids 2014;33:185-91.
10. Doherty M, Jansen TL, Nuki G, Pascual E, Perez-Ruiz F, Punzi L, et al. Gout: why is this curable disease so seldom cured? Ann Rheum Dis 2012;71:1765-70.
11. Kuehn BM. Chronic disease approaches needed to curb gout's growing burden. JAMA 2018;319:1307-9.
12. Stack AG, Johnson ME, Blak B, Klein A, Carpenter L, Morlock R, et al. Gout and the risk of advanced chronic kidney disease in the UK health system: a national cohort study. BMJ Open 2019;9:e031550.
13. Dalbeth N, House ME, Horne A, Te Karu L, Petrie K, McQueen F, et al. The experience and impact of gout in Māori and Pacific people: a prospective observational study. Clin Rheumatol 2013;32:247-51.
14. Scheepers LEJM, Burden AM, Arts ICW, Spaetgens B, Souverein P, de Vries F, et al. Medication adherence among gout patients initiated allopurinol: a retrospective cohort study in the Clinical Practice Research Datalink (CPRD). Rheumatology 2018;57:1641-50.
15. Jennings CG, Mackenzie IS, Flynn R, Ford I, Nuki G, De Caterina R, et al. Up-titration of allopurinol in patients with gout. Semin Arthritis Rheum 2014;44:25-30.
16. Nuki G, Doherty M, Richette P. Current management of gout: practical messages from 2016 EULAR guidelines. Pol Arch Intern Med 2017;127:267-77.
17. Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Comparison of drug adherence rates among patients with seven different medical conditions. Pharmacotherapy 2008;28:437-43.
18. Bradley EH, McGraw SA, Curry L, Buckser A, King K, Kasl S, et al. Expanding the Andersen Model: the role of psychosocial factors in long-term care use. Health Serv Res 2002;37:1221-42.
19. Glasheen WP, Cordier T, Gumpina R, Haugh G, Davis J, Renda A. Charlson Comorbidity Index: ICD-9 update and ICD-10 translation. Am Health Drug Benefits 2019;12:188-97.
20. Day RO, Frensham LJ, Nguyen AD, Baysari M, Aung E, Lau A, et al. Effectiveness of an electronic patient-centred self-management tool for gout sufferers: a cluster randomised controlled trial protocol. BMJ Open 2017;7: e017281.
21. Doherty M, Jenkins W, Richardson H, Sarmanova A, Abhishek A, Ashton D, et al. Efficacy and cost-effectiveness of nurse-led care involving education and engagement of patients and a treat-to-target urate-lowering strategy versus usual care for gout: a randomised controlled trial. Lancet 2018;392:1403-12.
22. Counsell AB, Nguyen AD, Baysari MT, Kannangara DRW, McLachlan AJ, Day RO. Exploring current and potential roles of Australian community pharmacists in gout management: a qualitative study. BMC Fam Pract 2018;19:54.
23. Mikuls TR, Cheetham TC, Levy GD, Rashid N, Kerimian A, Low KJ, et al. Adherence and outcomes with urate-lowering therapy: a site-randomized trial. Am J Med 2019;132:354-61.

J Rheumatol 2020;47:313–5; doi:10.3899/jrheum.191150