The Economic Value of Genetic Testing for Tolerance of Allopurinol in Gout

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J Rheumatol 2017;44;717-719
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*The Journal of Rheumatology* is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.
Gout affects around 0.08% of the population globally and is the most common cause of inflammatory arthritis in men. Gout is associated with a considerable economic burden to healthcare systems; gout patients incur substantially greater direct healthcare costs compared to the healthy population. The indirect costs to society, such as loss of productive capacity, are also high. Notably, measures of disease activity including serum urate acid (SUA) levels, frequency of flares, and the presence of tophi have all been linked to higher costs. Evidence demonstrates that health-related quality of life (HRQOL) is lower in the gout population when compared with the healthy population, largely attributed to the painful flares and physical disability associated with the disease. The global burden of gout is rising; disability-adjusted life-years increased from 76,000 in 1990 to 114,000 in 2010. The rising burden of gout has led to calls to improve the management of gout across healthcare systems.

Longer-term treatment of chronic gout aims to reduce and maintain target SUA levels, which in turn reduces symptoms and the risk of patients developing painful and debilitating tophi. Urate-lowering therapy (ULT) is indicated for patients with tophi who are experiencing acute attacks and/or with radiographic changes of gout. ULT drugs either increase the rate of the removal of uric acid by the kidneys or block the production of uric acid. Allopurinol, a xanthine oxidase inhibitor, is recommended as the first-line treatment for patients with gout requiring a urate-lowering drug. While allopurinol is a preferred treatment, there are issues with toxicity that can result in suboptimal titration, reducing the likelihood of patients receiving the most effective dose. The HLA-B*5801 allele is linked to an increased risk of allopurinol-induced severe cutaneous adverse drug reactions (SCAR). Risk factors for SCAR include ethnicity, age, sex (female), higher doses, poor renal function, and cardiovascular disease.

In this issue of The Journal, Ke, et al present their findings on the cost-effectiveness of HLA-B*58:01 screening alongside allopurinol treatment versus the use of alternative urate-lowering drugs. Screening comes with a cost to the healthcare system, not just of the test, but also healthcare practitioner time to administer the test and interpret results. Screening presents an opportunity to prevent patients from being prescribed a treatment that may result in increased healthcare costs and a lower HRQOL as a result of SCAR, and therefore inform a more effective distribution of healthcare resources. There is a need for economic evaluation to compare costs and health benefits to inform decisions about whether such interventions offer value for money overall.

The Ke, et al study used a decision analytical model to assess the direct healthcare costs and health benefit, represented by quality-adjusted life-years (QALY), of genetic screening followed by allopurinol for non-carriers of HLA-B*58:01 compared to commonly used urate-lowering agents: benzbromarone without screening, febuxostat without screening, and allopurinol without screening in Taiwan. The study looked not only at patients with gout requiring ULT, but also at patients with chronic kidney disease. Applying a 1-year time frame and using a third-party cost perspective, probabilistic sensitivity analysis demonstrated that screening prior to allopurinol prescription was cost-effective in 70% of iterations if decision makers are prepared to pay threshold NTS800,000 (US$25,600 in 2015) to gain 1 QALY. To prevent 1 SCAR in the allopurinol-using population it was estimated that 461 patients needed to be screened for HLA-B*58:01. The authors concluded that screening offered good value for money in this population.

A strong association has been identified between the risk of allopurinol-induced SCAR and the presence of HLA-B*58:01 allele in the Han Chinese, Thai, Indian, and Korean populations. There is a paucity of evidence in the European population although limited evidence demonstrates that HLA-B*58:01 allele is a risk factor for allopurinol-induced SCAR in a European (Portuguese) population. However, because the prevalence of
HLA-B*58:01 is lower, the potential benefits of screening will be more limited. The economic evidence to date seems to support this: cost-effectiveness studies of HLA-B*58:01 screening in different populations show varied results. A Korean study determined it would be likely to be cost effective and offered value for money. Favorable results were also identified in a Thai population, with screening identified as a potentially dominant intervention (i.e., both cheaper and more effective than the alternative). Mixed results were found by subgroups in a US-based population, with screening identified as being cost-effective for Asian and African American populations but not for the white or Hispanic ones. Finally, a study focusing on the Singapore population concluded that screening was not cost-effective. No cost-effectiveness studies were found through targeted literature searches that were published on other populations, likely due to a lack of clinical evidence.

The Ke _et al_ study is an example of stratified medicine (also known as personalized or precision medicine). Stratified medicine refers to the use of biomarkers to stratify patient populations into subgroups who are more likely to experience a benefit, or at higher risk of experiencing an adverse reaction to a treatment. A systematic literature review of economic evaluations of pharmacogenetic tests to reduce the incidence of adverse drug reactions found allopurinol was one of a small number of treatments with robust cost-effectiveness evidence available, albeit in a limited number of countries. Stratified medicine is relatively new, and consequently there are still challenges with conducting economic evaluations in this area, such as identifying where in a patient pathway the pharmacogenomic test best fits, the use of surrogate endpoints, and identifying robust clinical evidence for all comparators.

Currently only the American College of Rheumatology guidelines recommend HLA-B*58:01 screening prior to allopurinol prescription, but for a select group of patients (e.g., Koreans, Han Chinese, and Thai regardless of renal function). European guidelines did not recommend blanket screening because of a recognized lack of cost-effectiveness data to support screening in populations with a lower prevalence of HLA-B*58:01. Instead they recommend that physicians use their judgment, according to patient characteristics, to decide whether screening may be beneficial.

Future research is needed to determine whether screening is effective in a population with lower allele prevalence. It is important that studies cover a sufficient sample size to accurately estimate the burden and potential benefits in relation to adverse events that may affect only a small subgroup of the population. Once this is available, cost-effectiveness studies can be conducted to determine whether such interventions could be cost-effective uses of healthcare resources. Cost-effectiveness evaluations will also need to be done carefully according to potential variations in screening uptakes and how testing fits into the patient pathway: these differences lead to structural uncertainty in economic models and without detailed investigation can limit the interpretation of results in economic evaluations. It is also important to remember that healthcare systems (e.g., costs of care and resources used) vary greatly, a condition that limits the generalizability of economic evidence between countries. When additional robust clinical and economic evidence is available, decision makers will be better able to consider whether screening offers value for money for their population. Achieving greater knowledge of efficient and cost-effective treatment options could help to reduce or slow the growing burden of gout.

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J Rheumatol 2017;44:717–19; doi:10.3899/jrheum.170200