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COMMENTARY

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Treatment for hyperuricemia and gout in Japan: Aspect of prescription and duration

Di Zhang MM

Rehabilitation Medicine Center, Zhongshan Hospital, Fudan University, Shanghai, China

Correspondence
Di Zhang, MM. Zhongshan Hospital Fudan University, 180 Fenglin Road Shanghai, China 200032.
Email:zhangdi123192@163.com

Comment on "Akari S, et al. The reality of treatment for hyperuricemia and gout in Japan: a historical cohort study using health insurance claims data"

Uric acid is the end-product of purine metabolism in humans. A number of factors are involved in determining serum uric acid levels including age, sex, renal function, and dietetic factors such as fructose, purine, and alcohol intake. Conditions of excessive purine intake, endogenous defects in purine metabolism, and/or inadequate uric acid excretion lead to hyperuricemia, defined as serum uric acid ≥6 mg/dl (360 μmol/L) in women and ≥7 mg/dl (420 μmol /L) in men. Gout may occur when serum uric acid exceeds a certain level and infiltrates into the space of joints.[1] The prevalence of hyperuricemia was 13.3% in China,[2] 20.0% in the United States,[3] and 19.1%–25.0% in several European countries.[4] Recent reports of the prevalence and incidence of gout vary widely according to the population studied and methods employed but range from a prevalence of <1%–6.8% and an incidence of .58–2.89 per 1000 person years.[5]

Beyond the classic clinical manifestations, and irrespective of their presence, a number of epidemiologic studies have reported a relation between serum uric acid levels and a wide variety of association with hypertension, coronary heart disease, diabetes mellitus, preeclampsia, and chronic kidney disease.[6–9] The prevalence of hyperuricemia is significantly higher in patients with hypertension, diabetes, hyperlipidemia, coronary heart disease, and heart failure than in the general population. Compared with general population, patients with hyperuricemia or gout also have a higher prevalence of these diseases. This suggests that these comorbidities are interacting and exacerbating the progression of another condition. A retrospective, cross-sectional study using a Japanese health care database reported that the accurate prevalence of hyperuricemia in the Japanese population was 26.8% in male subjects and .9% in female subjects. In both male and female subjects, the prevalence of hyperuricemia in those with hypertension, diabetes, hyperlipidemia, higher BMI, or those with a smoking habit was higher than in those without these conditions.[10] The high prevalence and serious impact of hyperuricemia and gout have brought huge burden to the national medical and health system, so it is important to increase awareness of hyperuricemia in society and reduce the burden of hyperuricemia related diseases.

To examine specific characteristics and the reality of treatment of hyperuricemia or gout in Japan, Akari S and colleagues conducted a retrospective, longitudinal, historical cohort study[11] using the JMDC Claims Database, which constructed based on monthly claims from medical institutions and pharmacies, consisted mainly of company employees and their family members, and enabled researchers to estimate the prevalence of disease considering both of the diagnosis and the prescriptions for the respective treatment. The primary evaluation population included 64 677 patients enrolled between September 2013 and September 2019, with an index diagnosis of hyperuricemia alone (n = 46 280), gout only (n = 14 519), or hyperuricemia and gout (n = 3878). The prescription rate of uric acid-lowering drugs (ULDs) was 41% in all newly-diagnosed hyperuricemia and/or gout patients, lower than the rate of antihypertensive drugs in hypertensives and antidiabetic drugs in diabetes mellitus. Patients with hypertension, diabetes mellitus and renal disease showed longer median duration and higher rate of treatment continuation at 12 months, compared with patients without these comorbidities. Meanwhile, women, younger and patients with BMI < 25 kg/m^2 also showed better treatment continuation duration, compared with men, older, and those with higher BMI.

Although only 41% of patients received ULDs, different prescription rate existed among different groups of patients, with the lowest

being hyperuricemia group (38%), the middle being gout group (42%), and the highest being hyperuricemia and gout group (70%). This is consistent with the conventional wisdom that patients with hyperuricemia accompanied by the symptom of gout may be more necessary and eager to receive uric acid lower treatment. Prescription rate of ULDs for newly diagnosed patients in this study was largely in line with previous estimates from other countries, including Western Sweden (42%)[12] and New Zealand (41%),[13] higher than that in America (35%)[3] and Canada (22%).[14] It is important to note that compared with gout treatment guidelines in the United States[15] and Europe,[16] the Japanese guidelines[17] recommended more aggressive pharmacological treatment for asymptomatic hyperuricemia. Therefore, although the ULDs use in Japanese hyperuricemia or gout patients showed a non-inferiority coverage situation compared with other countries, Akari S and colleagues still believed that the prescription rate was relatively low. Some studies argued that asymptomatic hyperuricemia, which may be the cause or the consequence of comorbidities, may not require treatment because the benefits are modest.[18] Urate-lowering therapy initiation is not recommended in some guidelines in patients with asymptomatic hyperuricemia, even those with monosodium urate deposits. But joint deformity and compromised renal functions resulted from tophi in untreated chronic hyperuricemia also deserve consideration and caution. Therefore, while aggressive uric-lowering therapy may be beneficial to cardiovascular outcomes, more researches are needed to determine whether such a radical approach is desirable. However, optimal management of all comorbidities is of the utmost importance, irrespective of aggressive urate-lowering treatment.

There were also differences in the treatment continuation duration among patients with different uric acid conditions. Overall, the median duration of ULDs use among all subjects was 18 months, with a treatment persistence rate of 54.4% at 12 months. However, patients with asymptomatic hyperuricemia showed a more satisfactory duration than patients with gout. Since both hypertensives and diabetes mellitus showed higher continuation rate for antihypertensive drugs (66.7%) or antidiabetic drugs (74.9%) at 12 months. One condition that asymptomatic hyperuricemia group contained higher proportion of comobidities such as hypertension, diabetes and hyperlipidemia than other groups maybe a possible explanation. Unsatisfactory adherence was consistently observed and reported in many countries such as Ireland (46%),[19] Singapore (44%),[20] and UK (39%),[21] and even lower in China (22%).[22] The pooled overall adherence to ULDs (defined as taking >80% of the prescribed ULDs) analyzed in a systematic review of 24 studies published up to August 2016 was 46% worldwide.[23]

Another interesting and meaningful finding in this study[11] is the higher ULDs continuation rate at 12 months in overall study patients with versus without hypertension (76.8% vs. 42.6%) or diabetes (78.7% vs. 52.5%). The possible reason is that the improved effect of ULDs on blood pressure and insulin resistance may promote patients more inclined to continue treatment. Thus, the presence of comorbidities may possibly encourage hyperuricemia or gout patients to be more adherent to treatment due to increased awareness of its benefits and willingness to improve their overall health condition. A cross-sectional study to evaluate the relationship between medication adherence, serum uric acid levels with recurrent gout attacks conducted in 89 gout patients showed that, patients with diabetes were 1.5-fold more likely to be compliant to their ULDs compared to patients without.[24] A substantial amount of high-quality researches consistently showed that medication adherence to ULDs was significantly correlated with comorbidities including hypertension, diabetes, chronic kidney disease.[19,22,23] So concomitant use of ULDs and antihypertensives or antidiabetics may be beneficial to improve therapeutic effects and adherence to ULDs in patients with hyperuricemia and hypertension or diabetes. A retrospective cohort study[25] identified 13 341 patients with gout with incident allopurinol use found that adherent patients were 2.5-fold more likely than non-adherent patients to achieve an serum uric acid < 6.0 mg/dl (<360 umol/L). However, what calls for special attention for readers is that due to the lack of data, treatment effects including change of serum uric acid, blood pressure, glucose etc., and the reasons for treatment discontinuation or adherence were not evaluated. More rigorous studies are therefore requisite to confirm this hypothesis in beneficial of concomitant drugs usage. Obstacles to effective ULDs lie in perspectives of both patients and strategy providers. Patients who do not adhere to treatment may be frustrated with treatment strategies and unwilling to continue treatment because of poor outcomes. From the perspective of patients, maybe it's important to raise their awareness of the disease itself and the risk of other comorbidities. Treatment providers also need to take practical measures to support patients to manage their health condition, including applying knowledge of gout and management guidelines proficiently, providing appropriate and effective treatment strategy and urging patients to have regular follow-up clinic visits and physical examinations.

One of the limitations of the study[11] was that the population included in this study may not reflect a broad range of socioeconomic backgrounds. However, compared with the medical system, this database includes health care information with minimal geographic or occupational bias. What's more, the results of the study could not be generalizable to population aged >65 years because of the characteristics of the study population. Since the employment-based insurance covers various large-scale, nationwide industries, the database's strong and stable information collection ability ensures that the study can reflect the reality of treatment for hyperuricemia and gout in Japan to some extent.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

ORCID

Di Zhang MM https://orcid.org/0000-0002-9082-8455

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