The reality of treatment for hyperuricemia and gout in Japan: A historical cohort study using health insurance claims data

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Abstract
Hyperuricemia causes gout and has also been associated with metabolic syndrome and cardiovascular disease. Uric acid-lowering drugs (ULDs) are used to reduce uric acid levels for the treatment of hyperuricemia and gout. However, there is a lack of robust and real-world data on the history and treatment of patients with newly diagnosed hyperuricemia or gout in Japan. This retrospective, longitudinal, historical cohort study determined the characteristics of patients with hyperuricemia and/or gout, and prescription of, and adherence to, ULDs using data from the JMDC Claims Database. The primary evaluation population included 64,677 patients with newly diagnosed hyperuricemia and/or gout. Of these, only 26,501 (41.0%) had a prescription for ULDs at diagnosis. Even when ULDs were prescribed, the persistence rate of prescriptions declined over time, with a 54.4% persistence rate for ULDs at 12 months after the index diagnosis. In subgroups of patients with or without hypertension and diabetes, the rate of ULD prescription continuation was significantly higher in those with comorbidities than in those without (76.8% vs. 42.6% in those with vs. without hypertension, and 78.7% vs. 52.2% in those with vs. without diabetes). These findings suggest that therapeutic interventions to lower serum uric acid levels are under-utilized for patients with newly diagnosed hyperuricemia and/or gout in Japan.

KEYWORDS
database, gout, historical cohort, hyperuricemia, uric acid

1  |  INTRODUCTION

The number of patients with gout and hyperuricemia is increasing worldwide¹,² and in Japan.³ Hyperuricemia has been reported to be associated not only with gout⁴,⁵ but also with metabolic syndrome and cardiovascular diseases, including hypertension, dyslipidemia, diabetes, obesity, and chronic kidney disease (CKD).⁶–¹³

Uric acid-lowering drugs (ULDs) are used to treat hyperuricemia and gout, and consist of two main types of medication: uric acid production inhibitors and uricosuric agents. Several recently published database studies conducted in Japan have reported on the reality of medical treatment for hyperuricemia and gout.¹⁴–¹⁶ Koto and coworkers reported that severe renal dysfunction was the most important risk factor for failure to achieve target serum uric acid levels, that gout and asymptomatic hyperuricemia are often treated with low-dose ULDs, and that gout management in Japan may be suboptimal because many patients fail to achieve the target serum uric acid level.¹⁵,¹⁶

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FIGURE 1  Overview of study design

Higa and coworkers reported that the accurate prevalence of hyperuricemia in the Japanese population was 26.8% in male patients and 0.9% in female patients, arguing that it is also important to increase awareness of hyperuricemia in society and reduce the burden of hyperuricemia-related diseases.\(^{14}\) However, because these studies were cross-sectional, the actual history and treatment of patients with newly diagnosed hyperuricemia or gout remain unclear. Therefore, this study was designed to examine specific characteristics and the reality of treatment in individuals with a first diagnosis of hyperuricemia or gout using the JMDC Claims Database,\(^{17}\) a Japanese health insurance claims database.

2  | METHODS

2.1  | Study design

This retrospective, longitudinal, historical cohort study (UMIN000045426) was based on the JMDC Claims Database. An overview of study design is provided in Figure 1. All data were anonymized, de-identified, and compliant with the International Conference on Harmonization guidelines regarding the protection of human patients in observational studies.\(^{18}\) The study received ethical approval from the Ethics Committee of Research Institute of Healthcare Data Science: approval No. RI20200007.

2.2  | Data source and patient selection

The JMDC Claims Database uses standardized disease classifications and anonymous record linkage.\(^{17}\) It provides information on the beneficiaries (including encrypted personal identifiers, age, sex, International Classification of Diseases 10th revision [ICD-10] diagnostic and procedural codes), and the name, dose, and the number of days supplied for prescribed and/or dispensed drugs. The database also includes clinical and laboratory data from annual health check-ups.

The database for this study ("total data period") was constructed based on monthly claims from medical institutions and pharmacies submitted from September 2013 to September 2019, which included approximately 6.67 million insured persons (aged 0–75 years), and consisted mainly of company employees and their family members. The inclusion period ("inclusion data period") was set from September 2014 to October 2017. The final study population included health insurance subscribers who were in the JMDC Claims Database over that period and met the following inclusion criteria:

1. Database registrations within the total data period.
2. Subscribers of the health insurance association registered in the database at the end of the total data period.
3. The first (oldest) diagnosis of hyperuricemia or gout ("index diagnosis") was within the inclusion data period.
4. Twelve months of observations were available retrospectively from the time of the index diagnosis.
5. No record of ULD prescription prior to the index diagnosis.
6. Age ≥ 20 years at the index diagnosis.

2.3  | Definitions

An index diagnosis of hyperuricemia was identified using the ICD-10 code E790, and an index diagnosis of gout was identified using the ICD-10 code M10 (see Table S2 for ICD-10 code definitions). ATC code definitions for ULDs are shown in Table S1. Comorbidities were defined as the presence diagnoses at the time of the index diagnosis (see Table S2 for ICD-10 code definitions). Hypertension, dyslipidemia, and diabetes mellitus were defined as diagnoses accompanied by a prescription for the respective treatment in an outpatient setting at the time of the index diagnosis (ATC codes used to define prescription history are shown in Table S3), as defined previously.\(^{14,19}\) This avoids issues with ICD-10 codes in the claim database not accurately reflecting clinical manifestations.

2.4  | Endpoints

This study was analyzed data to determine the following parameters for newly diagnosed patients with hyperuricemia or gout: baseline characteristics; actual treatment received; rate of continuation with ULD treatment.

Laboratory data were collected from the latest annual medical check-up performed prior to the index diagnosis. The expected duration of ULD treatment continuation was defined as the period from the
date of ULD prescription to the date of prescription plus the number of days of prescription minus one day. The actual duration of treatment continuation was defined as a condition in which the next prescription of a ULD was received no later than 90 days after the end of the expected duration of medication because prescriptions for chronic conditions in Japan are often issued to provide drug supply for 60–90 days of treatment. Lack of treatment continuation was defined as the period of treatment that continued until the last scheduled date of medication during the continuation of treatment. The same definitions were also applied to other treatments.

2.5 Statistical analyses

Categorical variables were expressed as numbers and percentages. Continuous variables were expressed as mean ± standard deviation. The rate of treatment continuation was estimated using the Kaplan-Meier method. All statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA). In all analyses, a two-sided p-value of < 0.05 was considered statistically significant.

3 RESULTS

3.1 Study participants

The JMDC Claims Database population included 6,671,294 individuals enrolled between September 2013 and September 2019. Of these, 152,974 patients had a first diagnosis of hyperuricemia or gout within the inclusion data period (September 2014 to October 2017), and 67,104 patients were retrospectively observed for 12 months from this first diagnosis. There were 65,830 patients who had no previous prescription record for ULDs prior to the index diagnosis, of whom 1,153 were aged < 20 years and were therefore excluded (Figure 2). Therefore, the primary evaluation population included 64,677 patients with an index diagnosis of hyperuricemia alone (n = 46,280), gout only (n = 14,519), or hyperuricemia and gout (n = 3,878) (Figure 2).

Most of the patients were male (89%) and aged between 40 and 64 years (70%) (Table 1). Liver disease, hypertension and dyslipidemia were common comorbidities (Table 1). More than half of all patients (59%) had no prescription for ULDs at the index diagnosis or in following month, while the remaining patients (41%) were prescribed ULDs over this period (Table 1). The prescription rate of ULDs was 38% in patients with hyperuricemia only, 42% in those with gout only, and 70% in patients with both hyperuricemia and gout (Table 1). Uric acid production inhibitors (xanthine oxidoreductase [XOR] inhibitors) accounted for the majority of ULD prescriptions (39%), and febuxostat was the most commonly used XOR inhibitor (Table 1). With respect to the prescription rate of concomitant medications, 23.9% of patients were using antihypertensives, 17.4% were taking lipid-lowering drugs, and 5.9% were using antidiabetic agents (Table 1).

3.2 Treatment continuation duration

Use of ULDs declined over time from the index diagnosis (Figure 3). The treatment continuation rate for ULDs in patients with newly diagnosed hyperuricemia and/or gout was 54.4% at 12 months after the index diagnosis (Figure 3A). This rate was significantly lower than the continuation rate for antihypertensive drugs in patients with hypertension (66.7%) or antidiabetic agents in those with diabetes (74.9%) (Figure S1). The ULD continuation rate was significantly higher in patients with hyperuricemia only compared with gout only or hyperuricemia + gout (Figure 3B). In addition, the ULD continuation rate was significantly higher in patients with versus without hypertension (76.8% vs. 42.6%; Figure 3C) or diabetes (78.7% vs. 52.2%; Figure 3D). Females versus males, older versus younger individuals, those with a
| Parameter | Overall \((n = 64 677)\) | Hyperuricemia \((n = 46 280)\) | Gout \((n = 14 519)\) | Hyperuricemia and gout \((n = 3878)\) |
|-----------|-----------------|-----------------|-----------------|-----------------|
| Age, years | 47.1±11.3 | 47.0±11.4 | 47.5±11.0 | 47.4±10.3 |
| Age group, n (%) | | | | |
| 20–39 years | 16 170 (25.0) | 11 894 (25.7) | 3436 (23.7) | 840 (21.7) |
| 40–64 years | 45 081 (69.7) | 31 900 (68.9) | 10 305 (71.0) | 2876 (74.2) |
| ≥65 years | 3426 (5.3) | 2486 (5.4) | 778 (5.4) | 162 (4.2) |
| Sex, n (%) | | | | |
| Male | 57 758 (89.3) | 40 875 (88.3) | 13 148 (90.6) | 3735 (96.3) |
| Female | 6919 (10.7) | 5405 (11.7) | 1371 (9.4) | 143 (3.7) |
| Follow-up duration, months | 36.5±13.8 | 36.5±13.9 | 36.6±13.6 | 36.8±13.3 |
| Comorbidities, n (%) | | | | |
| Hypertensiona | 16 643 (25.7) | 13 378 (28.9) | 2636 (18.2) | 629 (16.2) |
| Dyslipidemiab | 12 525 (19.4) | 10 331 (22.3) | 1755 (12.1) | 439 (11.3) |
| Diabetes mellitusc | 4051 (6.3) | 3373 (7.3) | 589 (4.1) | 89 (2.3) |
| Angina | 2905 (4.5) | 2340 (5.1) | 466 (3.2) | 99 (2.6) |
| Acute myocardial infarction | 419 (0.6) | 346 (0.7) | 62 (0.4) | 11 (0.3) |
| Intracerebral hemorrhage | 174 (0.3) | 144 (0.3) | 22 (0.2) | 8 (0.2) |
| Cerebral infarction | 1061 (1.6) | 839 (1.8) | 168 (1.2) | 54 (1.4) |
| Heart failure | 3395 (5.2) | 2792 (6.0) | 506 (3.5) | 97 (2.5) |
| Atrial fibrillation and flutter | 1196 (1.8) | 953 (2.1) | 199 (1.4) | 44 (1.1) |
| Malignant tumor | 2266 (3.5) | 1819 (3.9) | 369 (2.5) | 78 (2.0) |
| Renal disease | 6377 (9.9) | 5425 (11.7) | 760 (5.2) | 192 (5.0) |
| Liver disease | 17 388 (26.9) | 14 517 (31.4) | 2252 (15.5) | 619 (16.0) |
| Uric acid-lowering medications, n (%) | | | | |
| None | 38 176 (59.0) | 28 554 (61.7) | 8443 (58.2) | 1179 (30.4) |
| Uric acid production inhibitors | | | | |
| XOR inhibitors | 24 908 (38.5) | 16 904 (36.5) | 5485 (37.8) | 2519 (65.0) |
| Allopurinol | 6776 (10.5) | 4484 (9.7) | 1548 (10.7) | 744 (19.2) |
| Febuxostat | 16 585 (25.6) | 11 337 (24.5) | 3656 (25.2) | 1592 (41.1) |
| Topiroxostat | 1788 (2.8) | 1202 (2.6) | 356 (2.5) | 230 (5.9) |
| Uricosuric drugs | 1852 (2.9) | 919 (2.0) | 696 (4.8) | 237 (6.1) |
| Benzbromarone | 1693 (2.6) | 873 (1.9) | 614 (4.2) | 206 (5.3) |
| Probenecid | 113 (0.2) | 25 (0.1) | 66 (0.5) | 22 (0.6) |
| Bucolome | 48 (0.1) | 21 (0.0) | 18 (0.1) | 9 (0.2) |
| Concomitant medications, n (%) | | | | |
| Antihypertensive drugs | 15 455 (23.9) | 12 812 (27.7) | 2122 (14.6) | 521 (13.4) |
| ACE inhibitors | 822 (1.3) | 689 (1.5) | 109 (0.8) | 24 (0.6) |
| ARBs | 10 233 (15.8) | 8547 (18.5) | 1347 (9.3) | 339 (8.7) |
| Calcium channel blockers | 10 084 (15.6) | 8227 (17.9) | 1457 (10.0) | 355 (9.2) |
| Diuretic drugs | 3044 (4.7) | 2633 (5.7) | 335 (2.3) | 76 (2.0) |
| Antihyperlipidemic drugs | 11 247 (17.4) | 9473 (20.5) | 1409 (9.7) | 365 (9.4) |
| Statins | 8448 (13.1) | 7106 (15.4) | 1082 (7.5) | 260 (6.7) |

(Continues)
BMI ≥25 versus < 25 kg/m², or patients with versus without renal disease had significantly higher rates of ULD continuation (Figure S2).

4 | DISCUSSION

There were two new findings in this study. Firstly, nearly half of patients with newly diagnosed hyperuricemia and/or gout did not receive a specific treatment to lower serum uric acid levels. Secondly, persistence with ULD therapy in these patients was worse than that for antihypertensive drugs in hypertension or antidiabetic drugs in diabetes mellitus, and the presence of both these comorbidities was associated with better persistence with ULD treatment.

The population of this study represented approximately 1% of the entire JMDC Claims Database, and the most common diagnosis was hyperuricemia. This result may that there are more patients with asymptomatic hyperuricemia than with gout in Japan. The Japanese guidelines do recommend pharmacological treatment for asymptomatic hyperuricemia in patients with serum uric acid levels of ≥8.0 mg/dl and complications such as kidney disease, urolithiasis, hypertension, ischemic heart disease, diabetes mellitus, metabolic syndrome, etc., or serum uric acid levels of ≥9.0 mg/dl. However, it remains to be determined whether ULD therapy can reduce event rates in patients with hypertension, ischemic heart disease, diabetes mellitus, metabolic syndrome etc. In contrast, the situation is different in the US and European Union. Based on the available data, the mean serum uric acid level in our study population was 7.69 mg/dl, reflecting the serum uric acid level at the time of the index diagnosis without therapeutic intervention. More than half of all patients (51.9%) with available data had a BMI of 25 kg/m² or higher, suggesting that hyperuricemia or gout may be closely related to obesity. This is consistent with the findings of previous epidemiological reports showing that the incidence of hyperuricemia increases with the presence of obesity and with increasing BMI.

Our study population had a lower rate of comorbidities, including hypertension, dyslipidemia and diabetes mellitus, compared with previous studies. This may be due to the differences of the definition in preexisting disease and the fact that patients in the current study had a new diagnosis of hyperuricemia and/or gout.

In patients with newly diagnosed hyperuricemia or gout, prescription of ULDS at the time of index diagnosis was relatively low, at 41%. In many cases, follow-up with lifestyle guidance was performed, and the rate of therapeutic intervention was limited. Poor adherence to ULDS has been reported previously which is consistent with the results of this study. It has also been reported that, in the United States, approximately 70% of prescription interruptions occur in patients newly started on ULDS. This may be due to insufficient understanding of the necessity to continue taking ULDS even in the absence of gouty arthritis, and lack of awareness of the need to prevent gouty arthritis. Thus, it may be that disease risk is widely recognized in hypertension and diabetes but not sufficiently recognized in hyperuricemia. In Japan, another study using the JMDC database has shown that controlling serum uric acid levels below 6.0 mg/dl, which is the target level for managing both hyperuricemia and gout, can suppress the occurrence of gout.

Epidemiological data showed that the risk of death in patients with hyperuricemia and gout was significantly reduced after more than 2 years of treatment with ULDS compared with an untreated group. However, it is still controversial as to whether ULDS should be used to treat asymptomatic patients with high serum uric acid levels.

Our finding that the presence of hypertension or diabetes markedly increased the rate of persistence with ULD treatment is consistent with previous data showing that adherence to treatment in patients with gout increases in proportion to the number of complications experienced. Epidemiologically, levels of uric acid and XOR have been reported to be independent risks factor for hypertension. The presence of elevated serum uric acid levels has also been reported to be associated with the risk of cardiovascular events in patients with hypertension, even when blood pressure is wellcontrolled. In addition, treatment with the XOR inhibitor topiroxostat in hypertensive patients with hyperuricemia has been shown to improve the urine albumin-to-creatinine ratio (UACR) and blood pressure. Furthermore, several meta-analyses have demonstrated that administration of allopurinol reduces blood pressure. Moreover, in...
FIGURE 3  Continuation of treatment with uric acid-lowering drugs (ULDs) for the overall study population (A), by treatment indication (B), and in patients with versus without hypertension (C) or diabetes mellitus (D). CI, confidence interval

the Framingham Heart Study, individuals with higher serum uric acid, including younger adults, are at a higher future risk of type 2 diabetes, independent of other known risk factors.\textsuperscript{41} Urinary uric acid clearance also appears to decrease in proportion to increases in insulin resistance in normal volunteers, leading to an increase in serum uric acid concentration.\textsuperscript{42} Thus, it appears that modulation of serum uric acid concentration by insulin resistance is exerted at the level of the kidney.\textsuperscript{42,43} A Japanese study in patients with hyperuricemia and diabetic nephropathy reported significant reductions in serum uric acid level and glycosylated hemoglobin in those treated with high-dose topiroxostat.\textsuperscript{44} Therefore, it may be beneficial to consider concomitant use of ULDs and antihypertensives or antidiabetics to improve therapeutic effects and adherence to uric acid-lowering therapy in patients with hyperuricemia and hypertension or diabetes.

This study has several limitations. First, the JMDC Claims Database only includes individuals insured by health insurance associations,
meaning that the population may not reflect a broad range of socioeconomic backgrounds. However, from a clinical point of view, this database includes all claims for members of all the health insurance societies for which the JMDC collects data, and enables patient-based tracking of visits and treatment flows even if the patient was transferred to another hospital during treatment or was completely cured, unlike databases sourced from medical institutions. Nevertheless, it does only cover a small subset of the Japanese population. In addition, the results of this study may not be generalizable to some sectors of the population, including the elderly aged ≥ 65 years, because the surveyed population does not include many patients in this age group, and information on those aged ≥ 75 years is completely lacking. Second, prescription history does not provide any information about whether a patient prescribed the medication actually took it. Third, we do not have any information on laboratory test results other than the annual check-up, and serum uric acid levels were determined based on information from one of these annual medical check-ups. Therefore, we were not able to follow the effects of treatment, including changes in serum uric acid levels, after the prescription of ULDs. However, this does not necessarily mean that clinicians who prescribed ULDs were not subsequently monitoring changes in serum uric acid during therapy. In addition, there is a possibility of bias because data on test results from specific medical check-ups can only be obtained from people who have undergone these tests. Finally, due to the lack of data, we were unable to assess the reasons for treatment discontinuation, which need to be clarified in future studies. This information could be useful in developing strategies to improve patient adherence to ULD treatment.

5 | CONCLUSIONS

Therapeutic interventions to reduce serum uric acid levels in patients with newly diagnosed hyperuricemia or gout are underutilized, and the rate of continuation with ULD treatment was lower than that for antihypertensive drugs in patients with hypertension or antidiabetic drugs in those with diabetes.

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AUTHOR CONTRIBUTIONS

Study conception and design: Seigo Akari, Takashi Nakamura and Kazuomi Kario. Data preparation: Seigo Akari. Data analysis and interpretation: Seigo Akari, Takashi Nakamura and Kazuomi Kario. Drafting and revising of the manuscript: all authors. Final approval of the submitted manuscript: all authors.

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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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