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Rheumatologists' understanding of refractory gout: a questionnaire survey in China

Xinxin Han, Yue Yin, Yu Cao, Xiaotian Chu, Yingdong Han, Hong Di, Na Xu, Yun Zhang* and Xuejun Zeng*

Abstract

Objective: To explore the understanding of refractory gout in Chinese rheumatologists.

Methods: We conducted an anonymous survey of rheumatologists attending an annual national academic conference on rheumatism.

Results: Of the 910 rheumatologists who completed the questionnaire, 751 (82.5%) had received relevant continuing medical education (CME). Of these, 140 (18.6%) rheumatologists did not select xanthine oxidase inhibitors as the first treatment for patients with chronic tophaceous gout. Of all respondents, 113 (12.4%), 251 (27.6%) and 324 (35.6%) prescribed incorrect maximum doses of allopurinol, febuxostat and benzbromarone, respectively; this tendency was more pronounced in the non-CME group. Most rheumatologists agreed that complications and comorbidities increased the difficulty of gout management and considered the term refractory gout to describe those cases with uncontrolled symptoms, unmet treatment targets or non-shrinkage of tophi after standardized drug treatment. Moreover, 62.8% (472/751) of specialists considered that a diagnosis of refractory gout was appropriate for patients whose lifestyle and compliance failed to improve despite adequate education and regular urate-lowering therapy.

Conclusions: Incorrect and inadequate drug therapy may contribute to some cases of refractory gout, especially in physicians without CME. An emphasis on non-drug therapy and the management of comorbidities and complications may reduce cases of refractory gout.

Department of General Internal Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing, P.R. China

*These authors contributed equally to this work.

Corresponding author:
Yun Zhang, Department of General Internal Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, No. 1 Shuaifuyuan, Dongcheng District, Beijing 100730, P.R. China.
Email: zykmpl@163.com

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Introduction

Gout is a common and curable form of inflammatory arthritis.[1] In 2015, the global prevalence of gout ranged from 1% to 4%[2] and was approximately 1.1% in mainland China.[3] As these figures continue to climb, new research and guidelines have rapidly emerged that have increased the understanding of gout. Inevitably, clinicians encounter some difficult cases in their daily practice. In 2011, the American College of Rheumatology (ACR) issued diagnosis and management recommendations for gout and hyperuricaemia that defined 'refractory gout' as 1) inability to achieve a serum uric acid (SUA) level of 6.0 mg/dL; 2) occurrence of recurrent flares despite apparently adequate treatment; 3) presentation of persistent and/or extensive tophaceous disease.[4] However, the frequency of flares and the duration of symptoms were not clearly defined. The concept of refractory gout remains vague and later guidelines contain no reference to the term. There is no universally accepted definition of refractory gout at present.

Refractory gout is a common problem faced by experienced rheumatologists. However, relevant research on the difficulties of gout treatment and rheumatologists' understanding of refractory gout is lacking.[5] Therefore, we conducted an in-depth investigation to examine the understanding of refractory gout in Chinese rheumatologists.

Methods

Subjects

Participants were recruited in November 2019 from rheumatologists attending the largest annual national academic rheumatism conference in China. Participants completed a study questionnaire and were divided into two groups according to their continuing medical education (CME). The questionnaire asked participants whether they had received CME about gout and hyperuricaemia, which involved studying previous diagnosis and treatment guidelines for gout (these guidelines included the 2012 ACR Guidelines for Management of Gout,[6] the 2018 European League Against Rheumatism Evidence-Based Recommendation: Diagnosis of Gout,[7] the 2018 Taiwan Multidisciplinary Consensus: Management of Gout and Hyperuricemia,[8] the 2016 Chinese Gout Diagnosis and Treatment Guide[9] and the 2017 Multidisciplinary Expert Consensus on the Diagnosis and Treatment of Hyperuricemia-Related Diseases in China[10]). Participants who answered 'no' to the question about CME were assigned to a non-CME group and those who responded 'yes' assigned to a CME group. All participants received information about the survey before completing the anonymous questionnaire, and all provided verbal consent. This study was approved by the ethics committee of Peking Union Medical College Hospital (S-K1088).

Data collection

The questionnaire design was based on a literature review and the suggestions of experts from the Chinese Association of Gout Study Group. A pilot study with 10 physicians was first conducted to analyse the validity of the questionnaire. The questionnaire contained 29 questions covering

the following four aspects (which comprised 8, 11, 6 and 4 questions, respectively): 1) general information about participants, namely, age, title, highest educational level, work unit, number of years working in the specialty, number of patients with gout admitted annually. 2) Perceived negative effects of the following complications and comorbidities on the treatment of gout: tophi, joint deformity, obesity, kidney stones, hypertension, diabetes, malignancy, renal insufficiency, liver insufficiency, ischemic heart disease and history of allergy to urate-lowering drugs. 3) Drug selection in difficult cases of gout: first-choice drugs, maximum daily dose and time required to achieve the target SUA concentration. 4) Participants' perceptions of what constitutes 'refractory gout' in terms of symptoms and signs, laboratory results, joint function and other influencing factors. The first three aspects were measured using single-choice questions and the fourth aspect was measured using multiple-choice questions. A Chinese online questionnaire platform was used to gather the data. Respondents had to complete all the questions before they could submit the questionnaire. Responses to the first three aspects of the questionnaire were compared between the CME and non-CME groups. Analysis of the responses to the fourth part of the questionnaire (conceptualizations of refractory gout) focused on participants who had received CME about gout.

Statistical analysis

The preliminary data were summarized using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA) and Adobe Illustrator CC 2015 (Adobe, San Jose, CA, USA). Frequency data were expressed as percentages, and interval data (e.g. age) were calculated and analysed using means and standard deviations. Student's t-test and the chi-square test were used to evaluate differences in background characteristics and drug selection between the CME and non-CME groups. The chi-square goodness-of-fit test was used to analyse differences in responses to the multiple-choice questions. A P-value of ≤ 0.05 was considered to indicate statistical significance.

Results

General information

A total of 1200 rheumatologists attended the whole conference and 910 rheumatologists from 28 provinces completed the study questionnaire (Figure 1). The response rate was 75.8% (910/1200). The participant distribution was consistent with that of rheumatologists in China. The mean age of respondents was 38.6 ± 8.2 years. Of all respondents, 77.5% worked in tertiary medical centres, 30.7% had more than 10 years of work experience and 33.5% saw more than 100 patients with gout a year. A total of 50.0% of respondents stated that they encountered 5% to 20% of difficult cases of gout in their daily work. Other features of the respondents' educational background and work experience are shown in Table 1.

Most of the respondents who worked in tertiary institutions and had more years of work experience had completed CME, so we grouped them accordingly. Participants in the CME group saw more patients with gout annually than those in the non-CME group ($P < 0.001$). When asked about the percentage of patients with refractory gout seen in daily consultations, most respondents in the CME group answered 5% to 20%, and most respondents in the non-CME group answered less than 5% (Table 1).

Medication use

For patients with chronic tophaceous gout and no contraindications, the first choice of

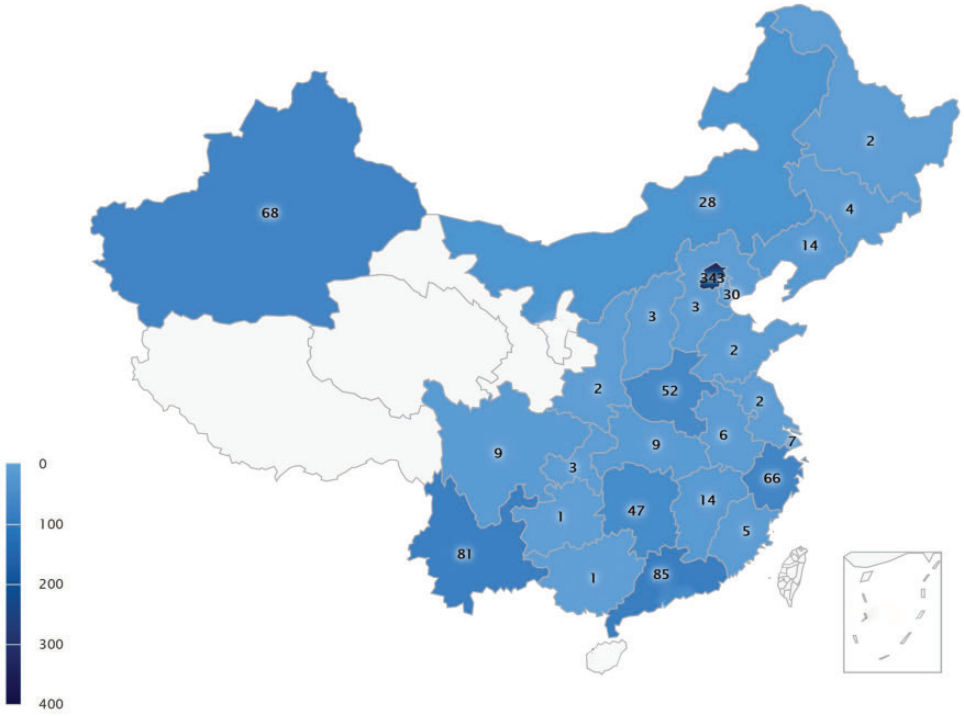

Figure 1. Distribution of participants.

770 (84.6%) rheumatologists was the xanthine oxidase inhibitors (XOI) allopurinol or febuxostat, whereas 129 (14.2%) preferred benzbromarone. A total of 140 (18.6%) rheumatologists did not select xanthine oxidase inhibitors as the first treatment. Of participants, 797 (87.6%), 659 (72.4%) and 586 (64.4%) gave the correct (guideline-recommended) maximum daily doses of allopurinol, febuxostat and benzbromarone, respectively, and 113 (12.4%), 251 (27.6%) and 324 (35.6%) did not.

A higher percentage of participants in the non-CME group compared with the CME group were unaware of the correct maximum daily dose of febuxostat (55.3% vs. 21.7%, $P < 0.001$) and benzbromarone (53.5% vs. 31.8%, $P < 0.001$) (Table 2).

Complications and comorbidities

Most rheumatologists agreed that complications and comorbidities increase the difficulty of gout management. The following complications and comorbidities were identified by most participants: renal insufficiency (857, 94.2%), followed by tophi (754, 82.9%), history of allergy to urate-lowering drugs (754, 82.9%), liver insufficiency (720, 79.1%), obesity (705, 77.5%), joint deformity (673, 74.0%) and diabetes mellitus (671, 73.7%) (Table 3).

A higher percentage of physicians in the CME group than in the non-CME group considered tophi ($P = 0.002$) and renal insufficiency ($P = 0.008$) to increase the difficulty of gout treatment. However, a lower percentage of physicians in the CME group

Table 1. Participant background characteristics.

	All groups (n = 910)	Non-CME group (n = 159)	CME group (n = 751)	*P*-value
Age (years)	38.6 ± 8.2	37.3 ± 8.1	38.9 ± 8.2	0.800
Associate chief physician and above (n, %)	387 (42.5)	53 (33.3)	334 (44.5)	0.002*
Master's degree or above (n, %)	521 (57.3)	75 (47.1)	446 (59.3)	0.013*
Type of hospital workplace				<0.001*
Tertiary medical centre (n, %)	705 (77.5)	88 (55.3)	617 (82.2)	
Secondary medical centre (n, %)	176 (19.3)	57 (35.9)	35 (4.7)	
Primary medical centre (n, %)	29 (3.2)	14 (8.8)	99 (13.2)	
Years of work experience				<0.001*
≤3 years (n, %)	314 (34.5)	138 (86.8)	176 (23.5)	
>3 years, ≤5 years (n, %)	124 (13.6)	8 (5.0)	116 (15.4)	
>5 years, ≤10 years (n, %)	193 (21.2)	3 (1.9)	190 (25.3)	
>10 years (n, %)	279 (30.7)	10 (6.3)	269 (35.8)	
Number of patients with gout seen annually				<0.001*
≤50 cases (n, %)	355 (39.0)	146 (91.8)	209 (27.8)	
>50 cases, ≤100 cases (n, %)	250 (27.5)	9 (5.7)	241 (32.1)	
>100 cases (n, %)	305 (33.5)	4 (2.5)	301 (40.1)	
Percentage of patients with refractory gout				<0.001*
≤5% (n, %)	380 (41.8)	104 (65.4)	276 (36.8)	
5% to 20% (n, %)	455 (50.0)	48 (30.1)	407 (54.2)	
>20% (n, %)	75 (8.2)	7 (4.4)	68 (9.1)	

*represents statistical significance.
CME, continuing medical education.

Table 2. First-choice drugs and maximum daily dose in patients with chronic tophaceous gout.

	All groups (n = 910)	Non-CME group (n = 159)	CME group (n = 751)	*P*-value
Preferred drug				
Allopurinol	216 (23.7)	53 (33.3)	163 (21.7)	0.003*
Febuxostat	554 (60.9)	74 (46.5)	480 (63.9)	<0.001*
Benzbromarone	129 (14.2)	29 (18.2)	100 (13.3)	0.132
Maximum dose/day				
Allopurinol ≥0.6 g	797 (87.6)	133 (83.6)	664 (88.4)	0.112
Febuxostat 80 mg	659 (72.4)	71 (44.7)	588 (78.3)	<0.001*
Benzbromarone 100 mg	586 (64.4)	74 (46.5)	512 (68.2)	<0.001*

All values are n (%); *represents statistical significance.
CME, continuing medical education.

than in the non-CME group considered obesity ($P = 0.047$), hypertension ($P = 0.015$) and diabetes ($P = 0.003$) to increase the difficulty of gout treatment (Table 3).

Conceptualizations of refractory gout

The understanding of refractory gout needs to be based on the mastery of standardized gout diagnosis and treatment. We asked

Table 3. Difficulties in gout treatment caused by complications and comorbidities.

Complications and comorbidities	All groups (n = 910)	Non-CME group (n = 159)	CME group (n = 751)	*P*-value
Tophi	754 (82.9)	118 (74.2)	636 (84.7)	0.002*
Joint deformity	673 (74.0)	118 (74.2)	555 (73.9)	1.000
Obesity	705 (77.5)	133 (83.6)	572 (76.2)	0.047*
Kidney stones	631 (69.3)	108 (67.9)	523 (69.6)	0.705
Hypertension	568 (62.4)	113 (71.1)	455 (60.6)	0.015*
Diabetes	671 (73.7)	132 (83.0)	539 (71.8)	0.003*
Malignancy	522 (57.4)	93 (58.5)	429 (57.1)	0.791
Renal insufficiency	857 (94.2)	142 (89.3)	715 (95.2)	0.008*
Liver insufficiency	720 (79.1)	117 (73.6)	603 (80.3)	0.068
Ischemic heart disease	569 (62.5)	94 (59.1)	475 (63.2)	0.367
History of allergy to urate-lowering drugs	754 (82.9)	126 (79.2)	628 (83.6)	0.202

All values are n (%); *represents statistical significance.
CME, continuing medical education.

rheumatologists in the CME group (n = 751) about their perceptions of the concept of refractory gout from two aspects: drug treatment-associated refractory gout and non-drug treatment-associated refractory gout.

Drug treatment-associated refractory gout

Most participants considered the concept of refractory gout to describe those patients whose symptoms cannot be controlled with standardized drug treatment. Most participants (730, 97.2%) thought that it was difficult to treat patients who had two or more flares a year while on standardized urate-lowering therapy (ULT). Of participants, 473 (63.0%) believed that recurrence of symptoms after initiation of ULT and preventive medications indicated refractory gout; 421 (56.1%) participants thought that recurrence of symptoms despite maximal nonsteroidal anti-inflammatory drug administration indicated refractory gout and 313 (41.7%) considered symptomatic recurrence in the course of ULT titration starting from a small dose to indicate refractory gout.

A total of 392 (52.2%) participants considered that failing to achieve target SUA after 3 to 6 months of standardized ULT indicated refractory gout. Of participants, 71 (10%), 209 (27.8%) and 79 (10.5%) rated the time required to reach the target as less than 3 months, 6 to 12 months, and more than 12 months, respectively. A total of 321 (42.7%) participants considered they were dealing with refractory gout if the SUA did not drop below 6 mg/dL after monotherapy, and 457 (61%) considered a diagnosis of refractory gout appropriate if there was non-shrinkage of tophi after more than 1 year of standard ULT.

Non-drug treatment-associated refractory gout

Joint destruction (96.0%), weak recovery of joints and surrounding muscles (63.0%) and existing inflammatory arthritis (67.9%) were considered the most important impediments to functional improvement and the main factors that increased

the difficulty of treatment ($P < 0.001$), whereas coexisting osteoarthritis (53.8%), traumatic injury (28.5%) and inadequate rest (26.5%) were considered less important. A total of 318 (42.3%) participants considered that joint destruction, weak recovery of joints and surrounding muscles and existing inflammatory arthritis could all affect the recovery of joint function.

A total of 472 (62.8%) participants considered a diagnosis of refractory gout appropriate if patients' lifestyle and compliance failed to improve despite adequate education and regular ULT. The main personal and social reasons for refractory gout were inadequate awareness of the disease (85.6%), inadequate self-discipline for lifestyle improvement (89.2%), poor compliance leading to irregular treatment (92.3%) and failure to use medication appropriately (72.6%) ($P < 0.001$). Lack of long-term physician follow-up (57.3%), limited therapeutic options (40.2%) and heavy financial burden (18.9%) were less important reasons.

Discussion

The concept of refractory gout was first proposed in a 1978 study of benzbromarone, which suggested that benzbromarone was suitable for patients with refractory chronic gouty arthritis who were allergic to probenecid or allopurinol.[11] Since then, refractory gout has been referred to but never clearly defined. In the 2011 ACR recommendations for the diagnosis and management of gout and hyperuricaemia, pegloticase was proposed as a potential treatment option for refractory gout. This was the first time refractory gout had been officially mentioned in a guideline.[6] However, pegloticase is not widely recommended in the guidelines, probably because it is expensive and not suitable for patients with glucose-6-phosphate dehydrogenase deficiency, of which there are more than 400 million worldwide.[12] Consistent with the present findings, the presence of tophi as a sign of refractory gout has become an inclusion criterion for clinical trials of refractory gout drugs.[13] To the best of our knowledge, this is the first study to investigate rheumatologists' perceptions of refractory gout in China.

Several guidelines recommend that the first-line treatment for gout should include XOI allopurinol or febuxostat;[11,14] second-line treatment may include uricosuric agents such as benzbromarone and probenecid. The 2011 ACR guidelines suggest that patients with refractory gout be treated with pegloticase.[6] In the present survey, some rheumatologists did not select XOI as first-line treatment, and several did not know the correct maximum dose of urate-lowering drugs. Therefore, it is unclear whether the cases these participants categorized as refractory gout were actually difficult to treat. Treatment difficulties caused by incorrect use of drugs or insufficient drug doses cannot be considered refractory gout. In 2006, our team conducted a questionnaire survey on the diagnosis and treatment of gout among physicians at different professional levels; we found that CME was the main factor that improved gout diagnosis and treatment.[15] In the present study, more physicians in the CME group than in the non-CME group knew the correct maximum daily dose of urate-lowering drugs, suggesting that CME increases physicians' understanding of these drugs. Experienced physicians with more CME were more confident about managing treatment difficulties caused by comorbidities and complications such as hypertension, diabetes and obesity, and were more aware of the correct use of urate-lowering drugs. They were also able to identify features of severe gout such as tophi and renal insufficiency,[6] and to focus on the essential features of refractory gout.

In 2016, 88 rheumatologists with an interest in gout from several countries established the preliminary remission criteria for gout using Delphi. SUA level was identified as an important measure of the treatment target. A consensus for the time frame to achieve the SUA target was established after three Delphi rounds; 58% of rheumatologists chose 6 months, 36% chose 1 year and 6% chose 3 months,[16] which is consistent with our survey results. When asked how long it should take to achieve the target for refractory gout, 52% of our participants answered 3 to 6 months and 28% responded 6 to 12 months. However, compared with the international panel of experts, our physicians assumed a shorter time frame to reach the target, which could affect the conceptualization of refractory gout by Chinese physicians. Fels and Sundy have suggested that refractory gout is usually associated with delayed or inadequate drug administration.[17] Therefore, physicians should adhere to the recommended length of treatment, strengthen patient follow-up and establish both physician and patient confidence in treatment. These measures may reduce the use of the label 'refractory gout'.

Interestingly, many physicians believe that failure to improve lifestyle and compliance is an important cause of gout treatment difficulties.[18] A British study that compared nurse-led gout care and usual general practitioner-led care in long-term treatment of patients with gout over a period of 2 years found that nurse-led gout care was associated with better compliance in patients with gout, better treatment outcomes and lower costs.[19] Therefore, specialists should pay more attention to patient lifestyle and compliance. As the field of general practice in China gradually develops and matures, specialists should cooperate with general practitioners to manage patients and improve patient compliance. Regarding the individual and social factors that increase the difficulty of gout treatment, patient compliance, self-discipline and understanding of the disease were identified as important factors by most of our participants. A previous survey on medication compliance among patients with gout found that 40% to 50% of patients with gout took medication irregularly.[20] A study in China showed that 69.9% of patients with gout had poor compliance, which was often associated with poor prognosis.[21] Therefore, we believe that poor patient lifestyle and compliance are important factors that increase the difficulty of gout treatment. In the past, the term refractory gout often referred to persistent symptoms and inability to maintain target SUA levels after adequate drug treatment.[17] However, the guidelines have long emphasized non-drug treatment;[4,6] therefore, the definition of refractory gout is based on both pharmacological and non-pharmacological treatment. Improvements in refractory gout are largely dependent on non-drug therapy.

Gout often needs to be differentiated from other crystal arthritis conditions, especially pseudogout (calcium pyrophosphate deposition disease).[22] When gout treatment is not successful, it is important to consider the accuracy of diagnosis and the possibility of other associated arthritis conditions. However, few tertiary medical institutions in China have the facilities to perform arthrocentesis, making it difficult to manage this kind of patient. Joint rehabilitation is another common concern among physicians. Previous studies have confirmed that long-term rehabilitation treatment in patients with gout can substantially improve the level of disease control.[23]

There is a small population of patients with gout whose treatment is challenging owing to genetic susceptibilities or other predispositions.[24] This population usually requires a higher drug dose or combined therapy as well as a protracted treatment

course, which may cause additional difficulties. However, a consideration of this population is beyond the scope of the present study, which was characterized by a low incidence of gout and strong focus on tertiary medical hospitals. Moreover, the findings of this preliminary study may not fully reflect the daily practice of rheumatologists or permit a conclusive definition of refractory gout. We plan to conduct future in-depth studies on specific problems in the treatment of refractory gout.

There were several study limitations. We found that although a substantial number of rheumatologists had received CME about gout, some of their medication treatment behaviours were inconsistent with the guidelines. The 'refractory gout' diagnosed by these rheumatologists may not be truly refractory, particularly if inadequate medication or insufficient medication doses were administered. More recent guidelines have emphasized the importance of non-drug treatment for patients with gout, which has not been mentioned in previous definitions or studies of refractory gout. In the absence of new disruptive drugs, our findings suggest that Chinese rheumatologists believe that comprehensive management of complications and comorbidities, enhanced patient education and lifestyle improvement may reduce the number of refractory gout cases.

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Author contributions

XZ, XH and YZ participated in the conception and design of the work. NX helped to optimize the research and designed the questionnaire. YY, XC, YH and HD played key roles in collecting the data. XH made substantial contributions to data analysis and manuscript drafting. YC, XZ and YZ critically revised the manuscript. All authors read and approved the final manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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ORCID iD

Xuejun Zeng https://orcid.org/0000-0002-6426-7586

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