The Impact of Initiating Dotinurad Urate-Lowering Therapy at Different Time Windows on Gout Flare Resolution Time: A Multicenter, Randomized, Parallel-Controlled Study

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CLINICAL PROTOCOL SYNOPSIS

Title	The Impact of Initiating Dotinurad Urate-Lowering Therapy at Different Time Windows on Gout Flare Resolution Time: A Multicenter, Randomized, Parallel-Controlled Study
Objectives	To confirm that initiating Dotinurad for uric acid reduction during the acute phase of gout is non-inferior to initiating it after the acute phase of gout has subsided, and to analyze whether initiating Dotinurad treatment during the acute phase will increase the pain level, the recurrence rate of gout, and the inflammatory level of patients. At the same time, to compare whether there are differences in the uric acid-lowering effects of initiating Dotinurad treatment at different times. And to evaluate the safety and tolerability of the treatment regimen.
Object of study	Patients with acute gout
Sample capacity	142 subjects
Inclusion criteria	• Male or female individuals aged 18-70 years old. • Meet the 2015 ACR/EULAR diagnostic criteria of gout. • With an onset of acute gout flares within 7 days. • With gout experiencing gout flares ≥2 times; or with gout experiencing gout flares 1 time and is younger than 40 years old; or with gout experiencing gout flares 1 time and has a serum uric acid level greater than 480 μmol/L and/or has co-morbidities (renal function impairment, hypertension). • Provide a signed written informed consent form.
Exclusion criteria	• Has secondary hyperuricemia. • Serum uric acid level < 360 μmol/L. • Used IL-1β inhibitors within 6 months before screening. • Used uric acid-lowering drugs within 1 month before screening. • Used anti-inflammatory drugs within 14 days before screening. • Comorbidities with nephrolithiasis or clinical urinary calculi • History of kidney transplantation or dialysis. • Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 . • AST or ALT > 2 times the upper limit of normal. • Systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 100 mmHg during the screening period. • White blood cell count < 3.5 × 10^9/L, or platelet count < 100 × 10^9/L, or

	hemoglobin < 90 g/L. • Currently in the treatment period of malignant tumors, or within 6 months after the end of the treatment period. • Congestive heart failure (New York Heart Association [NYHA] cardiac function classification II-IV), confirmed ischemic heart disease, peripheral artery disease and/or cerebrovascular disease (including patients who have recently undergone coronary artery bypass grafting or angioplasty). • Hypersensitivity to the study drugs or their excipients, or all of urine alkalinizer (potassium citrate/sodium citrate hydrate compound preparations). • Have active gastrointestinal ulcers/bleeding, or have had a recurrence of ulcers/bleeding in the past.
Study Design	This study is a multicenter, randomized, parallel-controlled, non-inferiority study aimed at confirming that initiating urate-lowering treatment with dotinurad during the acute phase of gout is non-inferior to initiating it after the acute phase of gout has been relieved in terms of the time to relief of gout attacks in subjects aged 18-70 years. Approximately 142 subjects will be randomly assigned to the experimental and control groups at a 1:1 ratio. The treatment group will receive dotinurad 2 mg qd, colchicine 1 mg qd, and etoricoxib 120 mg qd (days 1-3)/60 mg qd (days 4-7) for 4 weeks. The control group will receive, colchicine 1 mg qd, and etoricoxib 120 mg qd (days 1-3)/60 mg qd (days 4-7) for the first 2 weeks. Starting on day 15, the control group will receive dotinurad 2 mg qd and colchicine 1 mg qd for 2 weeks. If a subject's gout flare has not been relieved by day 7, etoricoxib will continue to be taken until relief is achieved.
Outcome Measure	Primary Outcome Measure Compare the days to resolution from enrolment to the resolution of an acute gout flare between the two groups. Secondary Outcome Measure Compare the main joint visual analogue scale (VAS) scores of the two groups on the 1, 3, 7 and 14 days. Compare the proportions of gout flares at 28 days between two groups. Compare the proportions of subjects whose serum uric acid (SUA) levels were ⩽ 360 umol/L at 7, 14 and 28 days between two groups. Compare the percentage reduction in SUA from the baseline at 7, 14 and 28 days between two groups. Compare the C-reactive protein (CRP) levels of the two groups at 7 and 14 days. Compare the erythrocyte sedimentation rate (ESR) levels of the two groups at 7

	and 14 days. Evaluate the safety of the two groups.
Statistic analysis	Statistical analysis dataset: Full Analysis Set (FAS): The set of subjects determined according to the intention-to-treat principle, including all subjects who were randomly assigned to the study, had used the investigational drug at least once, and had received efficacy evaluation after using the investigational drug. FAS is the main analysis dataset for subject distribution, demographics and baseline characteristics, and efficacy analysis. Per Protocol Set (PPS): Includes subjects who fully adhered to the protocol and had no serious protocol violations that affected the efficacy evaluation. PPS will be used for supplementary efficacy analysis. Safety dataset (SS): Includes all subjects who were randomly assigned to the study and had used the investigational drug at least once, and had received post-treatment safety evaluation. SS is the main analysis dataset for safety analysis. Population stratification will be finalized at the data review meeting. General principles for statistical analysis: Detailed statistical analysis methods will be described in the Statistical Analysis Plan (SAP), and the finalization and signing of the SAP should not be later than the database lock time. Continuous variables are described using mean, standard deviation, median, upper and lower quartiles, minimum value and maximum value. Count and categorical data are described using frequency and percentage. Decimal point rule: Unless otherwise specified, descriptive statistics such as mean, standard deviation, maximum value, and minimum value of continuous variables retain two decimal places; the frequency (percentage) of categorical or graded data retain two decimal places; test statistics and P-values retain three decimal places, and P-values less than 0.001 are expressed as "$p < 0.001$". Comparison of general conditions between groups will be analyzed using appropriate methods based on the type of indicators. Two-group comparison of quantitative data uses the paired t-test (normal distribution) or Wilcoxon rank sum test, intra-group comparison within quantitative data uses paired t-test (normal distribution) or Wilcoxon signed rank test, categorical data uses chi-square test or exact probability method (when the expected frequency in at least one cell is less than 5), and graded data uses Wilcoxon rank sum test (unadjusted for center effect) or CMH test (adjusted for center effect). Without special indication, statistical tests use two-sided tests, and a P-value less than 0.05 will be considered as a statistically significant difference.

	Statistical analysis of the primary endpoint: The primary endpoint was analyzed on the FAS. The Mann-Whitney U test was used for comparison between the groups. Hypothesis testing: For the experimental drug group and the control group, at a one-sided overall significance level, a non-inferiority test was conducted using the confidence interval method. Referring to the relief time of gout attacks in previous studies of 5.98-6.50 days 21-22, and considering the acceptance of patients in clinical practice, the non-inferiority threshold was set at 2. The upper limit of the 95% confidence interval of the difference in the primary endpoint between the two groups (positive control group - experimental drug group) was compared with the non-inferiority threshold of 2 to conduct the non-inferiority test. If the upper limit of the 95% confidence interval of the difference between the groups is less than 2, it is considered non-inferior to the positive control drug. H0: The difference in the time of acute gout attack relief between the experimental drug group and the positive control group is greater than or equal to 2; H1: The difference in the time of acute gout attack relief between the experimental drug group and the positive control group is less than 2. Statistical analysis of secondary endpoints: The statistical analysis of secondary endpoints is based on FAS and PPS. For the repeated measurement continuous secondary endpoints (percentage reduction in VAS and SUA from baseline), a repeated measures mixed-effects model (MMRM) was used for analysis, with group, center, visit, and the interaction effect between group and visit as fixed effects, and baseline VAS or baseline SUA as covariates and considering its interaction with visit; For categorical variables (proportion of gout recurrence, proportion of subjects with SUA level $\leqslant$ 360 umol/L), the inter-group comparison followed general principles, and the 95% confidence interval was calculated using the normal approximation method; For other biomarker-related endpoints (CRP, ESR), descriptive statistics were conducted, and the inter-group comparison followed general principles. Safety analysis: Evaluate the safety and tolerability of the two groups on the SS dataset.

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The Impact of Initiating Dotinurad Urate-Lowering Therapy at Different Time Windows on Gout Flare Resolution Time: A Multicenter, Randomized, Parallel-Controlled Study

I. Background

Gout is a crystal-related arthritis caused by the deposition of monosodium urate (MSU) crystals in the joints, and it is directly associated with hyperuricemia resulting from disorders of purine metabolism and/or reduced uric acid excretion. The prevalence of gout among Chinese adults is approximately 3.2%, and the number of gout patients increased from 5,971,855 in 1990 to 16,788,147 in 2021, with a trend towards younger age groups. In addition to joint damage, gout patients may also develop renal lesions and other manifestations of metabolic syndrome, such as hyperlipidemia, hypertension, diabetes, and coronary heart disease, imposing a heavy social burden.

The course of gout is divided into the preclinical phase (asymptomatic hyperuricemia and asymptomatic MSU crystal deposition) and the clinical phase (i.e., gout phase, which includes the acute gouty arthritis attack period, intercritical period, and chronic tophaceous gout period). Elevated serum uric acid levels are the fundamental cause of the occurrence and development of hyperuricemia, gout, and related comorbidities. When serum uric acid levels are too high, urate crystals deposit in the joints, leading to acute gouty arthritis attacks. After the acute gouty arthritis attack subsides, urate crystals and various immune-reactive cells can form tophi. Hyperuricemia not only leads to gout but is also associated with multisystem damage. Elevated serum uric acid acts as an intracellular pro-oxidant, inducing oxidative stress in cells, mitochondrial dysfunction, inflammatory responses, and activation of the renin-angiotensin system (RAS), leading to endothelial dysfunction, smooth muscle cell proliferation, interstitial inflammatory infiltration, and the development and progression of chronic kidney disease (CKD) and cardiovascular disease (CVD). Maintaining long-term serum uric acid levels within the target range can significantly reduce the frequency of gout attacks, prevent tophus formation, prevent bone destruction, slow renal impairment, lower mortality risk, and improve patients' quality of life, which is key to preventing gout and its related comorbidities. Therefore, urate-lowering drug therapy is very important.

The timing for initiating urate-lowering therapy (ULT) is not uniformly recommended across international and domestic guidelines. Some guidelines, such as the "Gout Diagnosis and Treatment Protocol," suggest that "since fluctuations in serum uric acid levels can trigger acute gout attacks, most previous gout guidelines have not recommended starting ULT during the acute phase of a gout attack. Instead, it is advised to consider using ULT after 2 weeks of anti-inflammatory and analgesic treatment." The "Chinese Guideline for the Diagnosis and Treatment

of Hyperuricemia and Gout (2019)" recommends "initiating ULT 2-4 weeks after the gout attack is controlled." In contrast, the "2020 American College of Rheumatology Gout Management Guideline" conditionally recommends "starting ULT during a gout attack if the decision is made to initiate ULT while the patient is experiencing a gout flare, rather than waiting until after the flare has resolved."

Some studies have shown that initiating urate-lowering therapy (ULT) during an acute attack can lead to better patient medication adherence. This is because starting treatment during the acute phase can reduce the number of times patients need to visit a doctor during the initial treatment period, bringing more convenience to their lives. It can also prevent patients from missing the opportunity to start standardized treatment due to lack of pain after the attack subsides and subsequent discontinuation of follow-up. Moreover, it allows for early normalization of serum uric acid levels, thereby building patients' confidence in treatment. This is of great significance for the management of gout patients. In recent years, several small-sample clinical trials have found that initiating ULT during an acute gout attack does not increase the duration of the attack, pain intensity, or recurrence rate of gout, and there are no significant differences in inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. However, there are still no clinical studies of high evidence grade on whether initiating ULT during the acute phase affects gout attacks.

Currently, the commonly used ULT drugs mainly include xanthine oxidase inhibitors (such as allopurinol and febuxostat) and uricosuric agents (such as benzbromarone). However, there are some potential safety issues associated with the use of these drugs. Allopurinol may cause hypersensitivity reactions, and studies have shown that these reactions are related to the HLA-B*5801 gene. Febuxostat may increase the risk of death in patients with cardiovascular disease, and therefore, warnings have been issued regarding this drug in countries such as the United States, Canada, and Japan. Benzbromarone has not been approved for marketing by the U.S. Food and Drug Administration (FDA) due to the potential for severe liver injury, and it has also been withdrawn from the market in several European countries. There is still a significant unmet need for ULT in clinical practice. Uric acid in the body is mainly excreted by the kidneys, and the urate transporter 1 (URAT1) plays an important role in renal urate reabsorption, making it an important target for ULT drugs. Dotinurad is a novel and highly selective URAT1 inhibitor that can effectively lower serum uric acid levels by inhibiting URAT1. This drug was approved in China in December 2024 for the treatment of gout with hyperuricemia. However, no studies have yet been published on the effects of Dotinurad treatment on acute gout attacks. This study aims to determine whether initiating Dotinurad for ULT during an acute gout attack will prolong the time to relief of the attack.

II. Study Objectives

To confirm that initiating Dotinurad for uric acid uric acid lowering during the acute phase of gout is non-inferior to initiating it after the acute phase of gout has subsided, and to analyze whether initiating Dotinurad treatment during the acute phase will increase the pain level, the recurrence rate of gout, and the inflammatory level of patients. At the same time, to compare whether there are

differences in the uric acid-lowering effects of initiating Dotinurad treatment at different times. And to evaluate the safety and tolerability of the treatment regimen.

III. Study method

A multicenter, randomized, parallel-controlled, non-inferiority study. The study is collaboratively completed by four sites.

IV. Eligibility

1、Inclusion criteria

- Male or female individuals aged 18-70 years old.
- Meet the 2015 ACR/EULAR diagnostic criteria of gout.
- With an onset of acute gout flares within 7 days.
- With gout experiencing gout flares ≥2 times; or with gout experiencing gout flares 1 time and is younger than 40 years old; or with gout experiencing gout flares 1 time and has a serum uric acid level greater than 480 μ mol/L and/or has co-morbidities (renal function impairment, hypertension).
- Provide a signed written informed consent form.

2、Exclusion criteria

- Has secondary hyperuricemia
- Serum uric acid level < 360 μmol/L.
- Used IL-1β inhibitors within 6 months before screening.
- Used uric acid-lowering drugs within 1 month before screening.
- Used anti-inflammatory drugs within 14 days before screening.
- Comorbidities with nephrolithiasis or clinical urinary calculi
- History of kidney transplantation or dialysis.
- Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2.
- AST or ALT > 2 times the upper limit of normal.
- Systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 100 mmHg during the screening period.
- White blood cell count < 3.5 × 10^9/L, or platelet count < 100 × 10^9/L, or hemoglobin < 90 g/L.
- Currently in the treatment period of malignant tumors, or within 6 months after the end of the treatment period.
- Congestive heart failure (New York Heart Association [NYHA] cardiac function classification II-IV), confirmed ischemic heart disease, peripheral artery disease and/or cerebrovascular disease (including patients who have recently undergone coronary artery bypass grafting or angioplasty).

• Hypersensitivity to the study drugs or their excipients, or all of urine alkalinizer (potassium citrate/sodium citrate hydrate compound preparations).
• Have active gastrointestinal ulcers/bleeding, or have had a recurrence of ulcers/bleeding in the past.

V. Study Design

1、Interventions

1.1 Administration and duration

Approximately 142 subjects will be randomly assigned to the experimental and control groups at a 1:1 ratio. The treatment group will receive dotinurad 2 mg qd, colchicine 1 mg qd, and etoricoxib 120 mg qd (days 1-3)/60 mg qd (days 4-7) for 4 weeks. The control group will receive, colchicine 1 mg qd, and etoricoxib 120 mg qd (days 1-3)/60 mg qd (days 4-7) for the first 2 weeks. Starting on day 15, the control group will receive dotinurad 2 mg qd and colchicine 1 mg qd for 2 weeks. If a subject's gout flare has not been relieved by day 7, etoricoxib will continue to be taken until relief is achieved.

1.2 Drug

Dotinurad will be provided in the form of 2 mg tablets, the dotinurad placebo will be provided in tablet form, colchicine will be provided as 1 mg tablets, and etoricoxib will be provided as 60 mg tablets.

2、Research period and visit schedule

2.1 Research period

The study lasts for 4 weeks (28 days). The study period is divided into four phases: Screening Phase (Days -6 to -1), Randomization (Day 0), Treatment Phase I (2 weeks), and Treatment Phase II (2 weeks).
Screening Phase
The screening phase shall commence no more than 6 days prior to randomization for subjects. During this period, informed consent will be obtained, and subject eligibility for enrollment will be assessed.
Randomization
On Day 0, subjects who meet all inclusion criteria and none of the exclusion criteria will be randomly assigned to either the treatment group or the control group.

Treatment Phase I

Starting from Day 1 of Treatment Phase I, subjects in the treatment group will receive 2 mg dotinurad once daily, 1 mg colchicine once daily, and etoricoxib at a dose of 120 mg once daily (Days 1–3) followed by 60 mg once daily (Days 4–7), for a total duration of 2 weeks.

Subjects in the control group will receive 1 mg colchicine once daily and etoricoxib at a dose of 120 mg once daily (Days 1–3) followed by 60 mg once daily (Days 4–7), for a total duration of 2 weeks.

Treatment Phase II

During Treatment Phase II, all subjects in both the treatment and control groups will receive 2 mg dotinurad once daily and 1 mg colchicine once daily for a continuous period of 2 weeks.

2.2 Visiting Plan

This study includes a total of 6 visits, scheduled during the screening period and on days 0, 3 (video visit), 7, 14 and 28.

3．Randomization

The study adopted the method of central stratified block randomization, randomly assigning subjects in a 1:1 ratio to the experimental group and the control group. The subjects were randomly assigned using the interactive web response system (IWRS). The randomization statistician generated the random tables of the subjects respectively using the PLAN process of SAS 9.4 or above version, and the systems engineer imported them into the IWRS system. The subject randomization table includes the subject randomization number and the corresponding group of the subject randomization number. After the successful screening of the subjects, the researchers from each center participating in this trial logged into the IWRS system to obtain the random numbers of the subjects.

4、Outcome Measures

4.1 Primary Outcome Measure

• Compare the days to resolution from enrolment to the resolution of an acute gout flare between the two groups.

4.2 Secondary Outcome Measure

• Compare the main joint visual analogue scale (VAS) scores of the two groups on the 1, 3, 7 and 14 days.

• Compare the proportions of gout flares at 28 days between two groups.

• Compare the proportions of subjects whose serum uric acid (SUA) levels were ≤ 360 umol/L at 7, 14 and 28 days between two groups.

• Compare the percentage reduction in SUA from the baseline at 7, 14 and 28 days between two groups.
• Compare the C-reactive protein (CRP) levels of the two groups at 7 and 14 days.
• Compare the erythrocyte sedimentation rate (ESR) levels of the two groups at 7 and 14 days.
• Evaluate the safety of the two groups.

Ⅵ、Statistical Analysis

1、Sample Size Estimation

The sample size was estimated using PASS 16 software. This study is a non-inferiority design, assuming equivalent efficacy between the treatment group and the active control group. Based on previous literature and clinical opinions, a non-inferiority margin of 2 and a standard deviation of 4 were used. Under the conditions of a one-sided significance level $\alpha = 0.025$ and power $1 - \beta = 80\%$, and a 1:1 ratio between the treatment group and the control group, it was estimated that 64 participants would be required per group. Considering a dropout rate of 10%, 71 participants would be needed per group, totaling 142 participants.

2、Statistical Analysis

Statistical analysis dataset:
Full Analysis Set (FAS): The set of subjects determined according to the intention-to-treat principle, including all subjects who were randomly assigned to the study, had used the investigational drug at least once, and had received efficacy evaluation after using the investigational drug. FAS is the main analysis dataset for subject distribution, demographics and baseline characteristics, and efficacy analysis.
Per Protocol Set (PPS): Includes subjects who fully adhered to the protocol and had no serious protocol violations that affected the efficacy evaluation. PPS will be used for supplementary efficacy analysis.
Safety dataset (SS): Includes all subjects who were randomly assigned to the study and had used the investigational drug at least once, and had received post-treatment safety evaluation. SS is the main analysis dataset for safety analysis.
Population stratification will be finalized at the data review meeting.
General principles for statistical analysis:
Detailed statistical analysis methods will be described in the Statistical Analysis Plan (SAP), and the finalization and signing of the SAP should not be later than the database lock time.
Continuous variables are described using mean, standard deviation, median, upper and lower quartiles, minimum value and maximum value. Count and categorical data are described using

frequency and percentage.

Decimal point rule: Unless otherwise specified, descriptive statistics such as mean, standard deviation, maximum value, and minimum value of continuous variables retain two decimal places; the frequency (percentage) of categorical or graded data retain two decimal places; test statistics and P-values retain three decimal places, and P-values less than 0.001 are expressed as "p < 0.001".

Comparison of general conditions between groups will be analyzed using appropriate methods based on the type of indicators. Two-group comparison of quantitative data uses the paired t-test (normal distribution) or Wilcoxon rank sum test, intra-group comparison within quantitative data uses paired t-test (normal distribution) or Wilcoxon signed rank test, categorical data uses chi-square test or exact probability method (when the expected frequency in at least one cell is less than 5), and graded data uses Wilcoxon rank sum test (unadjusted for center effect) or CMH test (adjusted for center effect).

Without special indication, statistical tests use two-sided tests, and a P-value less than 0.05 will be considered as a statistically significant difference.

Statistical analysis of the primary outcome measure:

The primary outcome measures was analyzed on the FAS. The Mann-Whitney U test was used for comparison between the groups.

Hypothesis testing: For the experimental drug group and the control group, at a one-sided overall significance level, a non-inferiority test was conducted using the confidence interval method. Referring to the relief time of gout attacks in previous studies of 5.98-6.50 days 21-22, and considering the acceptance of patients in clinical practice, the non-inferiority threshold was set at 2. The upper limit of the 95% confidence interval of the difference in the primary endpoint between the two groups (positive control group - experimental drug group) was compared with the non-inferiority threshold of 2 to conduct the non-inferiority test. If the upper limit of the 95% confidence interval of the difference between the groups is less than 2, it is considered non-inferior to the positive control drug.

H0: The difference in the time of acute gout attack relief between the experimental drug group and the positive control group is greater than or equal to 2;

H1: The difference in the time of acute gout attack relief between the experimental drug group and the positive control group is less than

2. Statistical analysis of secondary outcome measures:

The statistical analysis of secondary outcome measures is based on FAS and PPS.

For the repeated measurement continuous secondary outcome measures (percentage reduction in VAS and SUA from baseline), a repeated measures mixed-effects model (MMRM) was used for analysis, with group, center, visit, and the interaction effect between group and visit as fixed effects, and baseline VAS or baseline SUA as covariates and considering its interaction with visit;

For categorical variables (proportion of gout recurrence, proportion of subjects with SUA level $\leqslant$ 360 umol/L), the inter-group comparison followed general principles, and the 95% confidence interval was calculated using the normal approximation method;

For other biomarker-related outcome measures (CRP, ESR), descriptive statistics were conducted, and the inter-group comparison followed general principles.

Safety analysis:

Evaluate the safety and tolerability of the two groups on the SS dataset.

Ⅶ、Management of Gout Flares

After the initial gout flare has resolved, participants may experience subsequent acute gout attacks. These should be managed according to the investigator's clinical judgment and based on the participant's medical condition with appropriate short-term anti-inflammatory and analgesic treatment, including NSAIDs and corticosteroids. The use of these medications should be documented in the CRF.