



Metabolomics in Hyperuricemia and Gout

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Abstract: Urate is one of the key metabolites of purine metabolism, and the overproduction of urate in the liver or decreased excretion in the kidney in humans may lead to elevated levels of urate in the circulation, termed hyperuricemia (HU). The formation of monosodium urate (MSU) crystals in the joint or surrounding tissues may trigger inflammatory responses and gout attacks, which is the most common inflammatory arthritis. In addition to gout, HU has also been associated with many other metabolic diseases, such as cardiovascular disease, obesity, diabetes, fatty liver diseases, kidney diseases, hypertension, and various cancers. Overwhelming evidence indicates that HU and gout lead to systematic metabolic alterations underlying these metabolic disorders. As one of the most powerful omics techniques, metabolomics systematically analyzes all small-molecule metabolites in a biological system that directly reflect the physiological and pathological conditions. In recent years, metabolomics has been increasingly employed in clinical and experimental research in HU and gout. Emerging studies have developed predictive models to differentiate HU from gout based on metabolomics and machine-learning algorithms. In this review, we systematically summarize recent advances in metabolomic research in gout and HU in animal and human clinical studies. A comprehensive understanding of systemic metabolic changes caused by HU and gout may provide unprecedented insights into the pathological mechanisms in HU, gout, and related metabolic diseases, which may have a profound impact on the prevention, diagnosis, and treatment of HU and gout.

Keywords: gout; metabolomics; hyperuricemia; mass spectrometry; urate; metabolism; machine learning; biomarkers

1. Introduction

Gout is a common chronic inflammatory disease of the joint caused by the deposition of monosodium urate crystals (MSU) [1,2]. Epidemiological data show that the incidence of gout varies widely from <1% to 6.8% around the world [3]. Clinical evidence suggests that persistent hyperuricemia (HU) is a prerequisite for gout [4], which is diagnosed as fasting blood urate levels over 420 μ mol/L (7 mg/dL) in two separate days [5]. The increase of serum urate concentrations, HU, may be caused by multiple factors, such as upregulation of purine metabolism in the liver, increased dietary intake of purine, and/or impaired renal excretion. Gout flares are usually characterized by redness, swelling, heat, and pain in a single joint of the toes, ankles, and knee, and the inflammation resolves rapidly [6]. However, prolonged recurrent gout flares are often associated with the formation of tophi at the joint or extremity of the limb [7]. Urate lowering therapy (ULT) for HU or treatment of the inflammation by colchicine or non-steroidal anti-inflammatory drugs (NSAIDs) is the key to clinical gout management [8]. Gout and HU are often associated with multiple



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Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). metabolic co-morbidities, including hypertension, kidney diseases, cardiovascular disease, non-alcoholic fatty liver diseases, and various cancers [9,10].

Metabolomics is a relatively new omics technology that systematically identifies and quantifies all small-molecule metabolites in an organism [11,12]. As the substrates and products of biological activities, metabolites are essential for various cellular functions. Endogenous metabolites produced by the host organism and exogenous metabolites (xenobiotics) from microbiota, pharmaceuticals, or environmental chemicals constitute the entire metabolome, a collection of all metabolites. Emerging research has revealed that metabolites are not only the end products of biological processes, but also interact with the epigenome, transcriptome, and proteome [13–16]. For example, gout attacks triggered by MSU in the joints lead to systemic metabolic alterations. Previous studies found that MSU promotes GLUT1-mediated glycolysis that governs NLRP3 and interleukin-1 β activation on macrophages [17]. In addition, MSU regulates a unique JNK-dependent macrophage metabolic and inflammatory response [18]. In the progression of gout from HU, dynamic metabolic changes are often observed as a result of interplays among genetic factors, physiological status, and environmental insults. In this regard, traditional biochemical approaches focusing on a single or several metabolites to investigate such a complicated pathogenesis process in gout or HU may be inadequate. Thus metabolomic alterations could directly or indirectly reflect physiological and pathological states [19]. Therefore, metabolomics has become a powerful tool to investigate metabolic processes and identify disease-related biomarkers [20]. In recent years, innovative developments in analytic and bioinformatic technologies have greatly expanded the analytical capabilities of metabolomics to cover increasingly more metabolites at the systems biology level. Mass spectrometry (MS)-based analytical platforms provide powerful resolving capabilities for metabolomics [21], while bioinformatics tools provide deeper and broader insights for biological research [22,23].

The past decade has witnessed tremendous progress in understanding the pathophysiology of HU and gout, in which metabolomics plays an indispensable role (Figure 1). In this review, we summarize the advances of metabolomics studies on gout and HU. The challenges and future directions of metabolomics in this research area will also be discussed.



Figure 1. An overview of metabolomics studies in hyperuricemia and gout. Metabolomics studies are often performed using high-resolution mass spectrometry with multiple bioinformatics tools. In human clinical studies, metabolomics studies use saliva, serum, feces, and urine samples. Examples of some differential metabolites are shown with the different biological sources in gout and HU studies. HU is caused by urate overproduction in the liver or decreased excretion in the kidney, and MSU deposition in the joints triggers gout attacks. HU and gout are associated with multiple metabolic co-morbidities.

2. Analytical Technology for Metabolomics

The predominant analytical platforms used in metabolomics are nuclear magnetic resonance (NMR) spectroscopy or MS [24-26]. NMR provides an excellent tool for metabolite identification and quantification. The advantages of NMR are non-destructive analysis, a high reproducibility, and an unmatched structure-elucidation ability [27,28]. However, due to the limited sensitivity and absence of a proper separation system, NMR is currently overshadowed by MS in metabolomics analysis [25,29]. On the other hand, MS has been extensively used in metabolomics by being coupled with gas chromatography (GC) or liquid chromatography (LC) [12,19]. GC-MS is mainly used in the analysis of volatile (or volatile after derivatization) and thermally stable metabolites, whereas LC-MS is used to cover the majority of polar metabolites [30]. The columns used for LC separations can affect metabolomics analysis. For example, the LC columns based on hydrophilic interaction chromatography (HILIC) or C18 are widely used to separate aqueous metabolites, such as sugars [31,32], while the C8 column is good for the separation of less polar metabolites, such as free fatty acids [33,34]. Furthermore, the ionization mode, either in the positive or negative ion mode, may impact the coverage of metabolites as well. In general, basic metabolites are readily detected in the positive ion mode, whereas acidic compounds, such as fatty acids, are amenable for ionization in the negative ion mode. Thus, to improve the coverage of metabolomics analysis, both positive ionization and negative ionization are often performed, either in a separate acquisition or by switching between both modes within one method [31]. Furthermore, capillary electrophoresis (CE), ion mobility, and multidimensional LC provide supplementary separation techniques for LC-MS-based metabolomics [35,36]. Various mass analyzers, such as a quadrupole, ion trap, time of flight, Fourier transform ion cyclotron, and orbitrap, are used alone, in tandem or in combinations to trap, store, and resolve ions [37]. Given their high resolution, sensitivity, and throughput LC-MS-based approaches are capable of analyzing thousands of analytes simultaneously [21] and have therefore become the most popular techniques for metabolomics [38].

Multiple LC-MS strategies have been developed and routinely used for metabolomics. Dynamic multiple reaction monitoring (MRM)- and parallel reaction monitoring (PRM)based targeted and pseudo-targeted metabolomics possess a high sensitivity and reliable quantitation accuracy but limited coverage [39,40]. Untargeted strategies, such as datadependent acquisition (DDA) and data-independent acquisition (DIA), often based on high-resolution MS, have the best metabolite coverage but a compromised quantitation and reproducibility [41,42]. All the above approaches could perform a simultaneous qualification and quantitation of multiple metabolites. Thus, a combination of untargeted and targeted metabolomics approaches can provide a more comprehensive assessment of metabolites in a metabolome.

3. Metabolomics Data Analysis, Interpretation and Sharing

The diversity of metabolites, especially chemical structures with different regio- and stereoisomers, their natural abundance [43], and the different analytic approaches, as discussed above, present tremendous challenges to data analysis in metabolomics analysis. MS-based untargeted metabolomics data can be analyzed by a series of tools, such as xcms [44], MZmine [45], MS-DIAL [46], and skyline [47], to extract features of potential metabolite signals. To identify the features of metabolites, mass spectral databases are often used, such as the Human Metabolome Database (HMDB) [22], MassBank [48], GNPS [49], LipidBlast [50], and METLIN [51]. Traditional metabolite identification based on the exact mass, retention time, and MS/MS spectra similarity could appropriately annotate 12% of the total detected features in metabolomics analysis [52]. Molecular network-based metabolite identification, such as MetDNA [53], GNPS [52], and NetID [54].

Once metabolites are identified and quantified, metabolomics-based statistical analysis is often performed to uncover specific biological activities associated with metabolomic alterations. Differential metabolites of statistical significance are then discovered by traditional statistical hypothesis testing or recently developed machine-learning models to link certain metabolic alterations to phenotypic changes [13,55]. Bioinformatics-based analysis tools and databases are utilized to interpret large-scale and high-dimensional complex metabolomics data into a set of biological phenomena for biologists to understand, such as MetaboAnalyst [56], Kyoto Encyclopedia of Genes and Genomes (KEGG) [57], Small Molecule Pathway Database (SMPDB) [58] and HMDB [22]. Bioinformatics-driven metabolic pathway analysis no longer considers only a single or a limited number of metabolite changes, but rather the systematic disturbance of global metabolism [13]. This trend is reflected in the development of methodology from overrepresentation analysis (ORA) and quantitative enrichment analysis (QEA) [59] to network-based metabolomic pathway analysis [56,60]. Metabolomics analysis combined with other omics, such as genomics, transcriptomics, and proteomics, has attracted widespread research interest. Several multi-omics databases are available to enable the analysis of broader interactions and the correlation of metabolites with genes and proteins, such as Reactome [61] and Recon3D [62].

Big data analysis has been demonstrated to be efficient in biological and clinical research in other well-established omics techniques [63] and is currently under development in metabolomics [13]. Several insightful initiatives [64,65] and guidelines [12] have been proposed to standardize metabolomics data acquisition and reporting. Metabolomicsspecific data repositories, such as MetaboLights [23] and Metabolome Workbench [66], were recently established for metabolomics data deposition. These initiatives provide a way to conduct data sharing and re-analysis, but large-scale metabolomics data integration analyses across different platforms and laboratories are still limited and deserve future attention.

4. Metabolic Profiling and Metabolite Biomarker Discovery in Clinical Populations with HU and Gout

In large-scale clinical research, metabolomics is routinely applied to profile metabolic alterations in an attempt to uncover the pathological mechanisms and discover potential metabolite biomarkers [20]. Although HU is the major cause of gout, only a small fraction of HU patients experience gout flares, while a majority of patients (90%) remain asymptomatic. Currently, there is no reliable clinical approach for predicting HU patients who will develop gout. Metabolomics provides a novel tool to reveal metabolic alterations between HU and gout and has the potential to identify metabolite biomarkers for predicting the progression of HU to gout. In this regard, metabolomics has been performed in gout and HU patients to systematically profile their metabolic characterization compared to healthy controls (Table 1). Metabolites involved in amino-acid metabolism, lipid metabolism, purine metabolism, and energy metabolism have been discovered to be significantly different from healthy control in serum [31,67–69]. Other metabolic differences between HU and gout have been reported in recent metabolomics research, such as arginine biosynthesis, glycine, serine, and threonine metabolism, as well as some lipid metabolism [66,67]. Interestingly, some metabolites, such as those involved in tryptophan metabolism, neuroactive ligandreceptor interaction, and nitrogen metabolism pathway, were found to change at sequential gout progression stages [70], suggesting a role in the pathogenesis from HU to gout. The metabolomic observations in serum have been summarized in Figure 2 to provide a better overview of the altered pathways from controls to HU and gout. Similar alterations were observed in urine and fecal samples from gout patients [69,71,72]. Together, these global metabolomics profiles observed in metabolomics studies may reflect a pathological state and help to understand the underlying pathogenesis of HU and gout.



Figure 2. Venn diagram shows the up- and down-regulated metabolite biomarkers in serum of controls, HU, and gout. The orange text box denotes an increase in patients; the blue text box denotes a decrease in patients; and the yellow text box denotes metabolites reported by different articles with inconsistent trends.

To discover potential metabolite biomarkers for gout, especially in asymptomatic HU cohorts with a high risk of gout, it is essential to include large clinical cohorts in metabolomics studies with proper statistical models. In recent research, up to 547 cases were included, and multiple machine-learning-based models were applied to select the most predictable biomarkers from untargeted metabolomics data [70,73]. Apart from the traditional gout indicator, urate, several novel biomarkers, such as pyroglutamic acid, glycocholate, lactic acid, glutamate, bilirubin, 2-methyl butyryl carnitine, isoxanthopterin, and kynurenic acid, were identified. Notably, some of these reports validated their selected biomarkers in separate validation cohorts [69,70,73,74] or by other absolute quantitative approaches [70,74,75], which show a better potential for translation into an early clinical diagnosis in gout.

Date	Sample	Discovery Cohort	Validation Cohort	Technique Platform	Upregulated Biomarkers	Downregulated Biomarkers	Conclusions
2021 [31]	Serum	Gout (109) vs. healthy (119) Gout (109) vs. HU (102)		LCMS	Betaine, trigonelline, pipecolic acid,	Pyroglutamic acid, glycocholate, lactic acid, glutamate Glycocholate, uracil, myristic acid, arachidonate	Glycine, serine, and threonine metabolism disorder Arginine and proline metabolism disorder Ascorbate and aldarate metabolism disorder Alanine, aspartate, and glutamate metabolism disorder Arginine biosynthesis↑ Glycine, serine, and threonine metabolism disorder
2018 [67]	Serum	Gout (49) vs. healthy (50) Gout (49) vs. HU (50)		NMR	VLDL, isoleucine, leucine, glutamine, methionine, acetone, citrate, aspartate, creatinine, glucose, threonine, triglycerides, unsaturated lipids and phenylalanine VLDL, lipid, acetone, citrate, aspartate, glucose		Aminoacyl-tRNA biosynthesis↓ Valine, leucine and isoleucine biosynthesis↑ Nitrogen metabolism↑ Alanine, aspartate and glutamate metabolism↑ D-glutamine and D-glutamate metabolism disorder
2020 [68]	Serum	Gout (31) vs. healthy (31)		LCMS	4-hydroxytriazolam, bilirubin, urate, 4E,15Z-Bilirubin IXa, androsterone sulfate, 5a-dihydrotestosterone sulfate, etiocholanolone sulfate, epiandrosterone sulfate, 1,2-Di-O-(8-hexadecenoyl)-3-O- (6-sulfoquinovopyranosyl)glycerol, PE(22:5(4Z,7Z,10Z,13Z,16Z)/ 22:6(4Z,7Z,10Z,13Z,16Z,19Z))		Primary bile acid biosynthesis↓ Purine metabolism↑ Glycerophospholipid metabolism disorder
2020 [69]	Serum and Urine	Gout (30) vs. healthy (30)	Gout (50) vs. healthy (50)	LCMS	Pyroglutamic acid, Phe-Phe, 2-methylbutyryl carnitine		Purine metabolism disorder Branched-chain amino acids (BCAAs) metabolism disorder Tricarboxylic acid cycle disorder Synthesis and degradation of ketone bodies disorder Bile secretion disorder Arachidonic acid metabolism disorder
2018 [71]	Urine	Gout (35) vs. healthy (29)		GCMS	Urate, isoxanthopterin		Purine nucleotide synthesis↑ Amino acid metabolism↓ Purine metabolism↑ Lipid and carbohydrate metabolism disorder
2017 [72]	Feces	Gout (26) vs. healthy (26)		NMR	Alanine, glycine, taurine, succinate, acetate, a-glucose, b-glucose, a-xylose	Valine, asparagine, aspartate, citrulline, phenylalanine, a-ketoisocaproate	Urate excretion disorder Purine metabolism disorder Inflammatory responses disorder

Table 1. Metabolomic studies in human samples.

Validation Upregulated Downregulated Discovery Technique Date Sample Conclusions Cohort Cohort Platform Biomarkers Biomarkers TAG 18:1-20:0-22:1, TAG Gout (50) vs. Gout (69) vs. LCMS Lipid disorders 2021 [73] Serum HU (50) HU (50) 14:0-16:0-16:1 Glycerophospholipid metabolism disorder Tyrosine, phenylalanine, Árachidonic acid metabolism disorder arachidonic acid, stearic Sphingolipid metabolism disorder LCMS untargeted + acid, linoleic acid, oleic Linoleic acid metabolism disorder 2022 [75] Serum HU (20) vs. healthy (20) Lactic acid, valine, palmitic acid, targeted acid, lipids, LysoPC(18:0), α -linolenic acid metabolism disorder LysoPC(16:0), Phenylalanine, tyrosine, and tryptophan LysoPC(18:1(9Z)) biosynthesis disorder Phenylalanine metabolism disorder Gout (30) vs. healthy Urate, oxalic acid, L-homocysteic acid Gout (8) vs. healthy (15) 2017 [74] (30) CICMS + assay kits (HCA) Saliva Gout (8) vs. Urate, oxalic acid, L-homocysteic acid Gout (30) vs. HU (30) HU (15) (HCA) KYNA and 5-HIAA are related to acute kynurenic acid (KYNA), N1-Methyl-2-pyridone-5-5 sequential stages LCMS untargeted + inflammation of gouty arthritis 2022 [70] 5 sequential stages (347) 5-hydroxyindole acetic acid (5-HIAA), Serum carboxamide (200) targeted 2PY and 2AMIA are related to renal DL-2-Aminoadipic acid (2AMIA) (2PY) function damage caused by long-term HU

Table 1. Cont.

5. Multi-Omics and Big Data

The combination of metabolomics and other omics could provide comprehensive and novel insights into clinical and experimental research. Genotype-dependent metabolic phenotypes, such as urate and SLC2A9, 10-nonadecenoate (19:1n9)/10-undecenoate (11:1n1) and CYP4A, are discovered by analysis of GWAS with untargeted metabolomics [76,77]. There is a lack of aldehyde dehydrogenase 16A1 (ALDH16A1), which was discovered to be associated with serum urate levels and gout in humans [78] by potential interactions with hypoxanthine phosphoribosyltransferase 1 (HPRT1) [79]. In mice kidneys, significant changes in the transcriptional levels of cellular lipid metabolic genes and urate transporters as well as lipid profiles were consistent with metabolomics data [80], suggesting a potential role of ALDH16A1 and lipid metabolism in gout. Emerging data suggest that gut microbiota participate in purine and urate metabolism [81], crosstalk with the host immune system [82], and affect intestinal urate excretion [83,84]. Thus, in feces from gout patients, a combination of microbiome and metabolome analyses revealed an up-regulation of microbiota, such as Bacteroides, Porphyromonadaceae Rhodococcus, Erysipelatoclostridium and Anaerolineaceae, as well as altered metabolites involved in urate excretion, purine metabolism, and inflammatory responses [72]. A prospective cohort analysis of 105,703 UK Biobank (UKB) participants by targeted NMR metabolomics identified glycoprotein acetylation as a biomarker positively associated with the risk of incident gout and validated in 4804 non-overlapping participants [85].

6. Metabolomics in Experiment Models

Various animal models have been established for gout and HU research [86], and some of them have been used for metabolic studies. We summarized metabolomics studies in rodent models in Table 2.

Recently, an MSU crystal-induced gouty arthritis (GA) rat model was established by injecting an MSU crystals suspension (20 mg/mL) in the dorsal side of the right ankle. In this model, rat serum metabolomics profiling found that arachidonic acid, sphingolipid, and glycerophospholipid metabolism were significantly changed [87]. Consistently, in studies based on high fructose combined with a potassium-oxonate (HFCPO)-induced HU rat model, researchers used untargeted plasma metabolomics to find significant alterations between the HU group and control group. The differential metabolites included acylcarnitine and amino-acid-related metabolites [88]. In addition, urine samples have been widely used in metabolomics studies. In potassium-oxonate-induced HU rats, researchers used ¹H NMR and LC-MS to conduct nontargeted metabolomics studies in plasma and urine samples. They discovered 21 metabolites in plasma and urine to be closely related to HU, such as pyruvate, lactate, creatine, glycine, lysophosphatidylcholine (LysoPC), and phosphatidylcholine (PC) [89]. LC-MS using multiple reaction monitoring modes has been applied to detect the macrophage metabolic changes in an acute gouty peritonitis mouse model after MSU stimulation. They found that IL-37 might alter the macrophage polarization status by metabolic reprogramming, primarily by reducing TCA and several amino acids and oligopeptides [90].

Medical treatments for HU and gout, such as ULT and anti-inflammatory therapies, may have a significant impact on systematic alterations in metabolism. A recent study using CE-TOFMS metabolomics tested the hypothesis that Xanthine oxidoreductase (XOR) inhibitors exert organ-protective effects [91]. The metabolomics focused on the renal metabolites in a rat model of renal I/R and found that XOR inhibitors can preserve tissue-specific concentrations of some high-energy phosphates, such as ATP and ADP.

Data	Analytical Platform	Rodent Models	Differential Metabolites/ Metabolic Pathways
2022 [87]	UPLC-QTOF-MS/MS	MSU Crystal-Induced Gouty arthritis Rats	Arachidonic acid, sphingolipid, and glycerophospholipid metabolism
2021 [88]	UPLC-QTOF/MS	High fructose combined with potassium oxonate (HFCPO)-induced hyperuricemia Rats	Acylcarnitine and amino acid related metabolites
2020 [89]	¹ H NMR and UHPLC/Q-Orbitrap-MS	Potassium oxonate induced hyperuricemia rats	Pyruvate, lactate, creatine, glycine, LysoPC and PC and etc
2019 [91]	Capillary electrophoresis-time-of-flight mass spectrometry (CE-TOFMS)	Rat model of renal I/R	Purine/pyrimidine metabolism
2022 [90]	Shimadzu Nexera XR HPLC-MS SCIEX Triple Quad™ 3500	Acute gouty peritonitis mouse model	Glycolysis pathway

Table 2. Metabolomic studies in rodent models of HU and gout.

7. Summary and Future Directions

Gout and HU are closely associated with the dysregulation of multiple metabolic pathways. High-throughput omics techniques, such as metabolomics, have been increasingly recognized as indispensable tools to provide comprehensive insights at systems biology levels, which makes metabolomics a valuable tool for research on HU and gout. With a high coverage and large clinical cohorts, systematic metabolic alterations could be revealed. Thus, most of the metabolomics research in gout and HU focuses on profiling and discovering biomarkers in clinical studies. Some dysregulated metabolic pathways are found in the progression of gout, and multiple biomarkers are identified to differentiate different metabolic diseases. Recent years have witnessed the increasing integration of multi-omics studies in gout and related metabolic disorders. Particularly, some genetic variants are identified in GWAS studies, while gut microbiota and associated metabolites are also identified as risk factors for gout, which is deeply involved in metabolic alterations of the host. These findings have offered potential new strategies for the clinical prediction and treatment of gout. In clinical metabolomic studies, sample size, demographic characteristics and clinical parameters are key factors for identifying reproducible metabolites and pathways associated with metabolic diseases, including HU and gout. Furthermore, statistical analysis is important for omics analysis, covariates should be considered, and strict multiple hypothesis tests should be performed to minimize the risk of type 1 statistical errors.

Although tremendous progress has been made in recent years by applying metabolomics in gout and related research, the field still faces daunting challenges. First of all, the technology of metabolomics is still in its infancy. The coverage and repeatability of metabolomic studies remain unsatisfactory. On the other hand, standardized analytical methods and data-processing protocols have yet to be established, which hinders validation in clinical studies with different genetic, ethnic, and lifestyle backgrounds. Second, bioinformatics tools and databases for metabolomics are critical in data interpretation and mining. However, these tools for metabolomics remain underdeveloped compared with other relatively well-established omics techniques, such as genomics, transcriptomics, and proteomics, which makes them difficult to use in integrated omics studies. Third, the application of metabolomics in clinical gout research remains limited. More confirmatory studies should be performed in the future to validate metabolic profiling and biomarkers of gout with carefully designed clinical studies. Moreover, the development of bioinformatics tools and standardized protocols for sample collection, storage, preparation, quality control, and data reporting and sharing is instrumental in maximizing the power of metabolomics to understand the pathological mechanisms and developing metabolite biomarkers for HU, gout, and related metabolic diseases. Last but not least, multi-disciplinary efforts from basic sciences, clinicians, data processing, and policymakers are needed to ensure that the scientific findings in metabolomics benefit patients with HU and gout.

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