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Association between serum uric acid and inflammation in rheumatoid arthritis: Perspective on lowering serum uric acid of leflunomide

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ABSTRACT

Background: The association between serum uric acid concentrations and inflammation in patients with rheumatoid arthritis (RA) has been still controversial.
Methods: A total of 172 patients with RA who added leflunomide to methotrexate (MTX) in their treatment regimens were enrolled in this study. Twenty-seven RA patients taking MTX without leflunomide were also recruited in order to assess the fractional excretion of uric acid (FEUA).
Results: After leflunomide therapy for an average of 4.6 months, serum uric acid concentrations had significantly decreased compared to baseline concentrations ($p < 0.001$). Patients treated with a combination of MTX and leflunomide ($n = 23$) showed higher FEUA than those treated with only MTX ($n = 27$) ($p = 0.007$). Differences in serum uric acid concentrations after leflunomide therapy were significantly associated with those in serum creatinine concentrations (B coefficient = 3.081, $p < 0.001$), but not with those in acute phase reactants including ESR and CRP.
Conclusion: This study determined that leflunomide reduced serum uric acid concentrations through increased urinary excretion of uric acid, which might not reflect changes in disease activity status in RA. This implies that uric acid may not influence systemic inflammation in RA.

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1. Introduction

Uric acid is an end product generated by the metabolism of endogenous and exogenous purine in humans [1]. There is growing evidence that serum uric acid might play a crucial role in inflammatory responses. Soluble uric acid has been found to induce monocyte chemoattractant protein-1 (MCP-1) from vascular smooth muscle cells through activation of nuclear factor-κB (NF-κB) and p38 mitogen-activated protein kinase (MAPK) [2]. Production of proinflammatory cytokines, such as interleukin-1β (IL-1β), IL-6 and tumor necrosis factor-α (TNF-α), in human mononuclear cells are stimulated by uric acid [3]. An in vivo experiment demonstrated that uric acid has a potent ability as a proinflammatory molecule derived from dying cells [4]. In a population-based study, serum uric acid concentrations were shown to be closely associated with IL-6, C-reactive protein (CRP), and TNF-α [5,6]. These evidences suggest the possibility that uric acid could contribute to systemic inflammatory conditions such as rheumatoid arthritis (RA).

Leflunomide, an isoxazole derivative, is a commonly used, disease-modifying antirheumatic drug (DMARD) whose efficacy is comparable to that of methotrexate (MTX) in the management of RA [7]. Leflunomide selectively blocks dihydroorotate dehydrogenase (DHODH), a rate-limiting enzyme in the pathway of de novo pyrimidine synthesis [8,9]. A77 1726, an active metabolite of leflunomide, inhibits the proliferation of activated T lymphocytes in RA through the interruption of pyrimidine biosynthesis within lymphocytes [10]. Leflunomide alone or in combination with methotrexate was found to be therapeutically effective and safe in active RA patients throughout the progression of disease [11] due to its anti-inflammatory properties, including down-regulation of IL-1 and destructive enzymes such as matrix metalloproteinases [12]. Interestingly, some studies demonstrated that patients treated with leflunomide showed lower serum uric acid concentrations compared to baseline than those without leflunomide treatment [13–15]. Another study hypothesized that leflunomide's mechanism for lowering uric acid could be partially explained by renal handling of urate [14].

There are few data regarding the impact of serum uric acid on the clinical features of chronic inflammatory arthritis, including RA. Luczak et al. did not determine any correlation between serum uric acid concentrations and clinical outcomes of RA or undifferentiated arthritis [16]. In addition, serum uric acid concentrations were not associated with acute phase reactants, such as erythrocyte sediment rate (ESR) and CRP, in a cross-sectional study [15]. The primary objective of this study is to determine the effects of leflunomide on serum uric acid in the treatment of RA. In addition, we hypothesized that the changes in serum uric acid due to leflunomide would have an impact on disease

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activity in RA, considering the close interaction between uric acid and systemic inflammation of RA. Therefore, we also assessed whether changes in serum uric acid concentrations after leflunomide therapy reflected changes in acute phase reactants as well as other clinical and laboratory parameters.

2. Subjects and methods

2.1. Subjects

A total of 172 patients with RA who were treated with their first administration of leflunomide in addition to treatment with MTX-based anti-rheumatic drugs were consecutively recruited from the Rheumatology outpatient clinic in order to assess the correlation between changes in serum uric acid concentrations and other clinical and laboratory parameters. In addition, twenty-three of the 172 RA patients described above and an additional twenty-seven patients treated with MTX alone were enrolled in a study to assess the urinary excretion of uric acid. All enrolled patients met the classification criteria for RA proposed in 1987 by the American College of Rheumatology [17], and were >18 years old at the time of recruitment. Exclusion criteria included concomitant treatment with loop diuretics, thiazide, angiotensin II antagonist, fenofibrate, aspirin, and urate-lowering agents, such as xanthine oxidase inhibitors or benzbromarone, because these compounds interfere with renal urate handling. During leflunomide administration, concomitant medications were identified through a review of medical records and included methotrexate, sulfasalazine, hydroxychloroquine, azathioprine, and steroids. Among anti-rheumatic drugs for RA management, patients who were using cyclosporine and tacrolimus were also excluded from this study because these drugs are thought to increase serum uric acid through a reduction of uric acid in the renal tubules and because of their ability to inhibit glomerular filtration rate (GFR) [18]. The protocol of this study was reviewed and approved by the Institutional Review Board/Ethics Committee of The Catholic University Medical Center. All patients provided informed consent at the time of enrollment.

2.2. Collection of clinical data

General patient characteristics included age, sex, disease duration, height, weight, body mass index, smoking status (non-smoker vs. current smoker), and alcohol intake (non-alcoholic vs. current alcoholic). The presence of comorbidities, such as hypertension and diabetes mellitus, was identified from individual interview and review of medical records. Laboratory test data were retrospectively collected from both baseline (before the first leflunomide administration) and follow-up (after an average of 4.6 months of leflunomide administration). Routine serum laboratory tests included total cholesterol, triglyceride, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), uric acid, γ-glutamyl transferase (γ-GTP), total bilirubin, total protein, albumin, blood urea nitrogen (BUN), creatinine, ESR, and CRP.

Random spot urine was collected from each study population including twenty-three patients taking combination of MTX and leflunomide and 27 patients treated with MTX alone. The fractional excretion of uric acid (FEUA) was calculated as the following; FEUA (%) = (serum creatinine × urine uric acid) / (serum uric acid × urine creatinine). Renal function was assessed by estimated GFR using a predictive equation, the classic Cockcroft–Gault formula [19]. This study classified patients into two groups based on eGFR: <60 ml/min (n = 40) and ≥60 ml/min (n = 132).

2.3. Statistical analysis

Data were expressed as mean ± standard deviation (SD) for continuous variables and as a number (%) for categorical variables. The paired-sample *t*-test was applied to compare the differences in serum uric acid concentrations between baseline and after leflunomide therapy. Comparison of the differences in clinical and laboratory parameters between the 2 groups based on baseline eGFR (<60 ml/min and ≥60 ml/min) was performed using Student's *t*-test. The Mann–Whitney U-test was used to compare FEUA between patients treated with MTX alone and patients treated with a combination of MTX and leflunomide. Pearson's correlation analysis was applied to assess correlations between the difference in serum uric acid concentrations and other clinical and laboratory parameters. Multivariate regression analysis was subsequently used to determine risk factors for differences in serum uric acid concentrations; risk was described as odds ratios (ORs) and 95% confidence intervals (CIs). A $p < 0.05$ was considered to be statistically significant. All statistical analyses were carried out using the Statistical Package for the Social Sciences, ver 13.0.

3. Results

3.1. Baseline characteristics of enrolled subjects

A total of 172 patients with RA who were treated with their first addition of leflunomide to MTX were retrospectively reviewed in this study (Table 1). The mean age, percent of females, and mean disease duration were 58.2 years (SD 12.2), 76.7% (n = 132), and 8.8 years (SD 7.6), respectively. The mean follow-up duration between baseline and post-leflunomide therapy measurements was 4.6 months (SD 2.5). Other clinical and laboratory parameters, including smoking, alcohol intake, BMI, comorbidities, serologic biochemical tests, and acute phase reactants at baseline, are listed in Table 1.

3.2. Differences in laboratory parameters between baseline and leflunomide therapy

Between baseline and an average of 4.6 months of leflunomide therapy, decreased serum uric acid (4.5 ± 1.4 vs. 3.3 ± 1.2, $p < 0.001$ in

Table 1
Baseline clinical characteristics of enrolled study subjects (n = 172).

Variables	Values
Age (year)	58.2 ± 12.2
Sex, female	132 (76.7)
Disease duration (year)	8.8 ± 7.6
Smoking	17 (9.9)
Alcohol intake	25 (14.5)
Height (cm)	157.4 ± 0.6
Weight (kg)	55.8 ± 9.3
Body mass index (kg/m^2)	22.5 ± 3.2
Follow-up interval (months)	4.6 ± 2.5
Dosage of leflunomide (mg/day)	16.6 ± 4.7
Comorbidity	
Hypertension	29 (16.9)
Diabetes mellitus	22 (12.8)
Laboratory parameters	
Total cholesterol (mg/dl)	170.5 ± 33.5
Triglyceride (mg/dl)	105.5 ± 65.3
AST (IU/l)	20.5 ± 9.5
ALT (IU/l)	19.9 ± 13.8
ALP (IU/l)	180.1 ± 60.4
LDH (IU/l)	420.9 ± 116.1
Uric acid (mg/dl)	4.5 ± 1.4
γ-GTP (IU/l)	26.8 ± 24.7
Total bilirubin (mg/dl)	0.5 ± 0.2
Total protein (g/dl)	7.3 ± 0.5
Albumin (g/dl)	3.9 ± 0.3
BUN (mg/dl)	15.0 ± 5.0
Creatinine (mg/dl)	0.8 ± 0.2
ESR (mm/h)	48.2 ± 28.2
CRP (mg/l)	3.1 ± 3.1

Data were expressed as mean ± SD for continuous variables and n (%) for categorical variables.

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