Rheumatology International (2019) 39:1749–1757
https://doi.org/10.1007/s00296-019-04394-6

Rheumatology
INTERNATIONAL

OBSERVATIONAL RESEARCH

Serum uric acid increases in patients with systemic autoimmune rheumatic diseases after 3 months of treatment with TNF inhibitors

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Received: 30 May 2019 / Accepted: 22 July 2019 / Published online: 31 July 2019

Abstract

In patients with gout, the serum uric acid (SUA) is usually lower during acute gouty attacks than during intercritical periods. It has been suggested that systemic inflammatory response can cause this phenomenon. The objective is to determine whether therapy with TNF inhibitors (TNFis) affects SUA levels in patients with systemic autoimmune rheumatic diseases (SARDs) and whether SUA changes correlate with pro-inflammatory cytokines or with the oxidative stress marker allantoin. In this study, SUA, CRP, creatinine, MCP-1, IFN-α2, IFN-γ, Il-1β, IL-6, IL-8, IL-10, IL-12, IL-17a, IL-18, IL-23, IL-33, TNF-α, and allantoin levels were measured prior to and after 3 months of TNFis treatment in patients with SARDs. The values obtained in the biochemical assays were then tested for associations with the patients' demographic and disease-related data. A total of 128 patients (rheumatoid arthritis, $n=44$; ankylosing spondylitis, $n=45$; psoriatic arthritis, $n=23$; and adults with juvenile idiopathic arthritis, $n=16$) participated in this study. Among the entire patient population, SUA levels significantly increased 3 months after starting treatment with TNFis (279.5 [84.0] vs. 299.0 [102.0] µmol/l, $p<0.0001$), while the levels of CRP, IL-6, IL-8, and MCP-1 significantly decreased. Male sex was the most powerful baseline predictor of ΔSUA in univariate and multivariate models. None of the measured laboratory-based parameters had statistically significant effects on the magnitude of ΔSUA. 3 months of anti-TNF therapy increased the levels of SUA in patients with SARDs, but neither the measured pro-inflammatory cytokines nor the oxidation to allantoin appeared responsible for this effect.

Keywords Uric acid · Inflammation · Rheumatic diseases · Cytokines · Oxidative stress

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Introduction

Patients with gout tend to have lower SUA levels during an acute gout attack than during the intercritical period (i.e. the time between acute gout attacks) [1–3], but the mechanisms responsible for this phenomenon remain unclear. A drop in SUA levels was also observed during systemic inflammatory response (SIR) provoked by orthopedic surgery, suggesting that lowering in SUA concentrations is associated with SIR unrelated to gout [4]. Decreased SUA levels were also reported upon administration of human recombinant IL-6 to patients with refractory thrombocytopenia [5] implicating its causative effect. One study suggested that the decrease in SUA observed during an acute gout attack may be mediated by SIR-induced increase in urinary uric acid (UUA) excretion [6], while other study has failed to confirm this [4]. Circulating SUA might also be consumed in reactions with the free radicals generated during the SIR. Uric acid is the predominant antioxidant in the extracellular environment

[7–9] scavenging free radicals and thus preventing oxidative damage [10]. Despite the lack of uricase activity in humans [11], uric acid can be non-enzymatically oxidized into allantoin and other products by reactive oxygen species (ROS) [12]. During episodes of systemic inflammation, where oxidative stress is involved, levels of allantoin may rise as a consequence of more rapid oxidation of urate to allantoin. Allantoin has been used as a biomarker for monitoring oxidative status both in vitro and in vivo [13–16]. In this context, significantly increased levels of allantoin have been found in patients with active rheumatoid arthritis (RA) [16] and with gout [17] compared to healthy controls.

While in the setting of acute SIR, the levels of SUA seem to be inversely correlated with markers of inflammation, in a population-based study, SUA concentrations were shown to be positively correlated with IL-6, C-reactive protein (CRP), and TNF-α [18, 19]. Uric acid released by injured cells has been shown to be a damage-associated molecular pattern (DAMP) able to activate the inflammasome [20, 21] and to stimulate the production of pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, in human mononuclear cells [22, 23]. Interestingly, SUA levels were also found to be positively correlated with multiple pro-inflammatory cytokines released during severe exacerbations of malaria, and have been implicated in its pathogenesis [24]. This evidence suggests that uric acid could exert bidirectional effects in systemic inflammatory conditions such as RA. Of clinical importance, both chronic inflammation and hyperuricemia have been independently associated with increased cardiovascular risk not only in the general population or gout, but also in patients with systemic autoimmune rheumatic diseases [25, 26].

The aim of the present study was to investigate the effect of TNF inhibition on SUA levels in patients with systemic autoimmune rheumatic diseases (SARDs) including RA, ankylosing spondylitis (AS), psoriatic arthritis (PsA), and juvenile idiopathic arthritis (JIA). In addition, we assessed whether the ΔSUA concentration was associated with the levels of the most important pro-inflammatory cytokines concentrations as well as the oxidative stress marker allantoin.

Methods

Subjects

In this study, we used clinical data and frozen serum and plasma samples collected at baseline and first follow-up (3 months) from a prospective cohort of 128 patients with clinically and serologically highly active SARDs (44 with RA, 45 with AS, 23 with PsA, and 16 with JIA) starting therapy with TNFis (cohort 1). The patients were treated between 2008 and 2017 at the Institute of Rheumatology, Prague and their clinical data were captured in the database of the Czech biologic's registry ATTRA. The ATTRA registry is a national prospective cohort study with mandatory registration for all patients with RA, AS, PsA, and JIA who start treatment with biologic agents. The ATTRA study was approved by the Czech Multicentre Research Ethics Committee (no. 201611 S300) and all of the subjects provided their written consent for the collection and storage of biological samples and clinical data prior to participation. All procedures were performed in accordance with the Declaration of Helsinki.

In the Czech Republic, treatment with TNFis is covered in cases of RA (and adult patients with JIA and polyarticular involvement) when the DAS28 exceeds 5.1 despite the availability of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), for PsA, if the disease is not adequately controlled with csDMARDs and, for AS, if the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) exceeds 4 and the CRP/ESR are elevated above typical healthy levels. Selected patients met the classification criteria. For AS, we have used New York criteria, for PsA either Moll and Wright criteria, or CASPAR criteria (either set was applicable). The diagnosis of RA and JIA was made by their treating physician, who was expected to apply the current ACR/ACR-EULAR or ILAR criteria, respectively. At baseline, these patients had highly active diseases (i.e. fulfilled the eligibility criteria for TNFis therapy) and also had CRP levels above 10 mg/l. Patient information including demographic parameters, disease activity, concomitant medications, and comorbidities was collected from the clinical questionnaire responses in addition to specific disease activity at 3 months post-clinical intervention.

In addition, to analyze the relationships between ΔSUA, UUA excretion, and the other parameters, urine spot samples were obtained from ten patients with SARDs (eight with RA, two with PsA) initiating TNFis between 2016 through 2017 (cohort 2). These patients were also selected using the criteria described above. This study was approved by the Institutional Ethics Committee of Institute of Rheumatology, Prague, Czech Republic (no. 10113/2016).

Laboratory analyses

In every case, sera and plasma were separated within 60 min of being drawn from the patients and then immediately aliquoted and frozen at − 80 °C until further biochemical analysis. All of the analytes were measured in serum collected before and after 3 months of TNFis treatment except for allantoin, which was analyzed in plasma.

The concentrations of serum CRP, creatinine, and SUA and UUA and urine creatinine were determined using the Beckman Coulter AU system with Beckman Coulter CRP

Latex, Creatinine (Enzymatic), and Uric Acid kits (Beckman Coulter, Brea, CA, USA). The CRP Latex Kit was calibrated for high sensitivity, according to the manufacturer's instructions.

We employed flow cytometry bead-based immunoassays (LEGENDplex™ Human Inflammation Panel, BioLegend, San Diego, CA, USA) to quantify the concentrations of pro-inflammatory cytokines (MCP-1, IFN-α2, IFN-γ, Il-1β, IL-6, IL-8, IL-10, IL-12p70, IL-17a, IL-18, IL-23, IL-33, and TNFα). Data were analyzed using Kaluza Analysis Software (Beckman Coulter).

To estimate UUA excretion (only in cohort 2), fractional excretion of uric acid (FeUA) was determined using the equation: (UUA/SUA) × (serum creatinine/urinary creatinine) × 100. The results are given in percentages.

Plasma allantoin levels were assessed using the Agilent Infinity 1290 system coupled with the Triple Quad 6460 tandem mass spectrometer (Agilent Technologies, Waldbronn, Germany). An ACQUITY UPLC BEH Amide Column (100 mm × 2.1 mm, 1.7 µm particle size) (Waters, Milford, MA, USA), thermostated at 30 °C, was used for the analysis. The mobile phases consisted of 0.1% formic acid in deionized water (solvent A) and 0.1% formic acid in acetonitrile (solvent B). The flow rate of the mobile phase was maintained at 0.4 ml/min. The optimized gradient program [(time (min))/volume% B] was 0/95, 1/95, 3/50, 4/20, 5/95, and 10/95. The injection volume was 2 µl, and the samples were kept at 5 °C. The tandem mass spectrometry measurement was performed in multiple reaction-monitoring mode using positive electrospray ionization. The precursor and product ions were *m*/*z* 159 and *m*/*z* 116, respectively (collision energy 5 V and fragmentor voltage 60%). The ion source was set as follows: gas temperature: 350 °C, gas flow: 10 l/min, nebulizer pressure: 310 kPa, and capillary voltage: 4000 V. For sample preparation, 300 µl of 100% acetonitrile was added to 100 µl of plasma, shaken (vortex), and centrifuged (10 min/14,000 rpm). 100 µl of supernatant was transferred into chromatographic vials. For the statistical analyses, the ratio between the values at baseline and those after 3 months of therapy with TNFis were used.

Statistical analyses

Data are summarized as means with standard deviation (SD) or as medians with interquartile range [IQR]. Medians are mostly used for laboratory measurements, whose distribution was skewed to the left. Baseline characteristics between diagnostic groups were compared using ANOVA and the Kruskal–Wallis test for continuous variables and Fisher's exact test for categorical ones. Changes in measurements from baseline and at 3 months after initiating TNFis treatment were evaluated using the Wilcoxon signed-rank test. For the exploratory analysis of changes in various interleukin concentrations, the *p* values from their respective Wilcoxon tests were corrected for multiple comparisons using the Benjamini–Hochberg method.

To explore the relationship between ΔSUA and various demographic and laboratory-based characteristics, first univariate and then stepwise multiple linear regression models were constructed to look for association with the patients' baseline characteristics (sex, diagnosis, age, BMI, and weight) and the significantly changing laboratory-based parameters. Laboratory-based predictors required log transformation for the sake of the model fit. The level of statistical significance was set to 0.05. All analyses were performed in the statistical language and environment R, version 3.5.0.

Results

Study population

We studied 128 patients (57 females, 45%) with a mean age of 43.9 (SD 14.5, range 18–81) years, who had started TNFis therapy. Their baseline characteristics are presented in Table 1. Diagnostic groups significantly differed in their proportion of females (patients with AS and PsA—lower percentage of females, patients with JIA and RA—lower percentage of males), in their age (patients with JIA and AS are younger than those with PsA and RA), slightly in their weight (biggest difference—patients with PsA weighed more than those with JIA), in their glucocorticoids usage (highest among patients with RA), and in their NSAIDs usage (highest among patients with AS, JIA, and PsA).

ΔSUA

As shown in Table 2, the levels of SUA in our patients were significantly lower before treatment with TNFis (279.5 [84.0] µmol/l) than after 3 months of treatment (299.0 [102.0] µmol/l, $p < 0.0001$) with a median difference of 19.0 [56.6] µmol/l.

Other laboratory-based parameters

Several laboratory-based parameters, namely, CRP (31.2 [26.7] vs. 2.3 [4.2] mg/l, $p < 0.0001$), IL-6 (62.0 [143.5] vs. 13.3 [24.7] pg/ml, $p < 0.0001$), IL-8 (82.9 [101.0] vs. 57.2 [62.5] pg/ml, $p = 0.0117$), and MCP-1 (962.6 [528.5] vs. 878.7 [457.2] pg/ml, $p = 0.0016$) were significantly higher at baseline than 3 months later. The concentrations of the remaining cytokines (IFN-α2, IFN-γ, Il-1β, IL-10, IL-12p70, IL-17a, IL-18, IL-23, IL-33, and TNFα) and of allantoin did not significantly differ as a result of TNFis treatment. Relative to baseline, serum creatinine levels

Table 1 Baseline characteristics for the cohort 1 ($n=128$) and for the four diagnostic groups

	n	Total	RA	AS	PsA	JIA	p value
		128	44	45	23	16	
Female	n (%)	57 (44%)	33 (75%)	7 (16%)	6 (26%)	11 (69%)	< 0.001*
Age (years)	Mean (SD)	43.9 (14.5)	56.4 (10.4)	35.4 (9.8)	46.7 (12.1)	30.0 (8.5)	< 0.001
Weight (kg)	Mean (SD)	74.2 (15.1)	73.6 (15.4)	73.5 (16.2)	81.3 (11.4)	67.7 (12.8)	0.0436
BMI (kg/m^2) ($N=80$)[a]	Mean (SD)	26.4 (4.8)	26.6 (5.4)	26.5 (4.7)	26.4 (4.5)	25.3 (4.0)	0.9936
CRP (mg/l)	Median [IQR]	31.2 [26.7]	22.5 [22.4]	40.6 [23.9]	23.4 [21.6]	44.8 [22.5]	< 0.001**
DAS28-CRP ($n=82$)[b]	Mean (SD)	5.79 (1.02)	5.99 (0.86)		5.17 (1.17)	6.14 (0.82)	0.003
BASDAI[b] ($n=40$)	Mean (SD)	n.a.		6.22 (2.13)			n.a.
Concomitant glucocorticoids	n (%)		33 (75.0%)	6 (13.3%)	6 (26.1%)	8 (50.0%)	< 0.001*
Concomitant NSAIDs	n (%)		11 (25.0%)	30 (66.7%)	12 (52.2%)	10 (62.5%)	< 0.001*
Concomitant COX-2 inhibitors	n (%)		2 (4.5%)	2 (4.4%)	0 (0%)	1 (6.3%)	0.738*
TNFis	Etanercept, n (%)	23 (18.0%)	15 (34.1%)	5 (11.1%)	1 (4.3%)	2 (12.5%)	0.038*
	Adalimumab, n (%)	42 (32.8%)	13 (29.5%)	17 (37.8%)	9 (39.1%)	3 (18.8%)	
	Infliximab, n (%)	43 (33.6%)	10 (22.7%)	19 (42.2%)	6 (26.1%)	8 (50%)	
	Golimumab, n (%)	18 (14.0%)	6 (13.6%)	4 (8.9%)	5 (21.7%)	3 (18.8%)	
	Certolizumab pegol, n (%)	2 (1.6%)	0 (0%)	0 (0%)	2 (8.7%)	0 (0%)	

Unless stated otherwise, Fisher's exact test in a one-factor ANOVA was used to determine group differences

n.a. not applicable

*p value from Fisher's exact test. For the TNFis, the p value was simulated without certolizumab pegol

**p value from Kruskal–Wallis ANOVA

[a]For 48 (38%) patients the data on weight and hence BMI were missing, most for AS (21.47%), and JIA (9.56%) patients

[b]DAS28-CRP is not measured for AS patients, BASDAI is measured for AS patients only

increased significantly after 3 months of TNFis treatment (68.0 µmol/l [21.0] vs. 73.0 [19.0] mg/l, $p<0.0001$) (Table 2).

Relationship between ΔSUA and patient parameters

The regression analysis showed that the ΔSUA was more pronounced in males (model estimate 32.5 µmol/l [55.5]) than in females (model estimate 6 µmol/l [56.0]) (Fig. 1). No other patients' baseline characteristics (diagnosis, age, BMI, weight) did have an influence on ΔSUA, neither univariately nor in the model together with sex.

Relationship between ΔSUA and laboratory-based parameters

In the univariate and multivariate regression models for predicting ΔSUA, no change over time in the (log-transformed) levels of CRP, pro-inflammatory cytokines, oxidative stress marker—allantoin, nor any change in the reported use of NSAIDs, conferred a statistically significant effect on the magnitude of ΔSUA (Fig. 2). The use of glucocorticoids (in the model together with sex) did not have an influence on ΔSUA.

Relationship between ΔSUA and change of FeUA in cohort 2

In cohort 2 (ten patients total: four males, six females; eight patients with RA, two with PsA), the levels of SUA were significantly lower at baseline than after 3 months of TNFis treatment (267.5 [133.3] vs. (342.5 [147.3] µmol/l, $p=0.0059$), but on a group level, there was no significant difference in FeUA before and after TNFis treatment (Table 2).

Discussion

To the best of our knowledge, this is the first study comprehensively evaluating the effect of treatment with TNFi on SUA level in patients with SARDs. We have observed an increase in SUA levels in the whole cohort with SARDs after abrogation of systemic inflammation using TNFis. These results correspond with an earlier report from Waldron et al. demonstrating that SUA levels decrease during SIR provoked by orthopedic surgery in patients without gout [4] or after administration of human recombinant IL-6 to patients with refractory thrombocytopenia [5]. Taken together, systemic inflammation and/or certain pro-inflammatory

Table 2 Laboratory parameters at baseline and after 3 months of therapy with TNFis

Analyte	Pre-TNFis treatment, median [IQR] or mean (SD)	Post-3-month TNFis treatment, median [IQR] or mean (SD)	Median difference between pre- and post-treatment values, median [IQR] or mean (SD)	*p* value*
SUA, µmol/l[a]	279.5 [84.0]	299.0 [102.0]	− 19.0 [56.8]	< 0.0001
Serum CRP, mg/l	31.2 [26.7]	2.3 [4.2]	27.0 [26.4]	< 0.0001
Serum creatinine, µmol/l	68.0 [21.0]	73.0 [19.0]	− 3.0 [9.0]	< 0.0001
IFN-α2, pg/ml, *n* = 93	101.4 [222.3]	103.3 [184.8]	5.4 [78.9]	0.3469
IFN-γ, pg/ml, *n* = 72	83.6 [354.5]	67.7 [208.8]	9.9 [123.7]	0.0830
IL-10, pg/ml, *n* = 95	5.2 [8.9]	5.1 [6.8]	0.3 [6.5]	0.3469
IL-12p70, pg/ml, *n* = 98	2.2 [3.9]	2.6 [3.4]	− 0.1 [2.6]	0.7129
IL-17a, pg/ml, *n* = 82	40.1 [55.3]	32.7 [54.7]	− 0.2 [31.2]	0.5032
IL-18, pg/ml, *n* = 95	112.6 [177.8]	112.8 [219.7]	5.5 [108.5]	0.4627
IL-1β, pg/ml, *n* = 100	31.0 [60.1]	30.6 [47.0]	2.6 [30.5]	0.3469
IL-23, pg/ml, *n* = 100	53.4 [108.4]	36.4 [79.7]	− 0.5 [48.5]	0.4083
IL-33, pg/ml, *n* = 99	32.5 [101.3]	29.4 [87.1]	0.8 [40.8]	0.3782
IL-6, pg/ml, *n* = 99	62.0 [143.5]	13.3 [24.7]	45.3 [140.1]	< 0.0001
IL-8, pg/ml, *n* = 99	82.9 [101.0]	57.2 [62.5]	10.8 [76.6]	0.0117
MCP-1, *n* = 101	962.6 [528.5]	878.7 [457.2]	119.8 [344.9]	0.0016
TNF-α, pg/ml, *n* = 95	16.8 [35.8]	18.4 [27.7]	0.7 [18.9]	0.3469
FeUA, *n* = 10	6.9 [5.4]	6.2 [3.8]	0.03 [4.5]	0.9219
Allantoin, *n* = 99			− 6.0 [255]**	
DAS28-CRP[b], *n* = 82	5.79 (1.02)	2.74 (1.05)	3.01 (1.15)	< 0.0001
BASDAI[b], *n* = 40	6.27 (2.07)	2.06 (1.45)	4.05 (2.49)	< 0.0001

*Wilcoxon signed-rank test was used to compare the difference between paired samples. In the exploratory analysis of interleukins changes, *p* values from their respective Wilcoxon tests were corrected for multiple comparisons using the Benjamini–Hochberg method

**For statistical analyses, the ratio between the values at baseline and values after 3 months of treatment with TNFi were used (1.030 [0.8455])

[a]The reference range of SUA is 208–428 µmol/l for men and 155–357 µmol/l for women. (1 mg/dl SUA = 59.48 µmol/l)

[b]DAS28-CRP is not measured for AS patients, BASDAI is measured for AS patients only

cytokines appear to have an impact on SUA levels in patients with gout as well as with other inflammatory conditions.

The mechanism underlying the decrease in SUA associated with systemic inflammation remains elusive. Urano et al. [6] reported that the SUA percentage upon onset of an acute gout attack correlated with CRP and IL-6 levels, as well as with increased UUA excretion, estimated by the percentage change in FeUA during the attack. In the present study, we analyzed the levels of CRP and 13 pro-inflammatory cytokines in patients with SARDs and did not observe any significant associations between the magnitude of the ΔSUA and the investigated cytokines or CRP levels.

We also measured FeUA in a small cohort of patients, which suggested that FeUA was not largely affected by TNFis treatment in this group. However, the small number of patients ($n = 10$) precluded us from drawing any firm conclusions on the relationship between ΔFeUA, ΔSUA, and other parameters of interest.

An alternative hypothesis to explain mechanism of SUA decrease during SIR involves the increased production of ROS during inflammation and the resulting degradation of SUA to allantoin [12]. In patients with Wilson's disease, an inherited disorder of copper metabolism characterized by the impairment of copper incorporation into ceruloplasmin and enhancement of oxidative stress, SUA levels were found to be markedly reduced, whereas levels of allantoin were elevated. The degradation of SUA by free radicals was proposed to be responsible for this phenomenon [27]. In the field of rheumatic diseases, both patients with active rheumatoid arthritis [16] and with gout [17] were reported to have significantly increased plasma levels of allantoin compared to healthy controls. We have analyzed allantoin as a stable biomarker of oxidative stress, but we have not found any correlation between the amount of the change of allantoin and the change of SUA or other analyzed parameters.

Interestingly, we observed more pronounced changes in SUA in males than in females. This phenomenon appeared not to be confounded by diagnosis (more males were represented in the AS and PsA groups), BMI or generally higher SUA levels in males. We can speculate that sex hormones may play a role in increased responsibility of SUA levels to

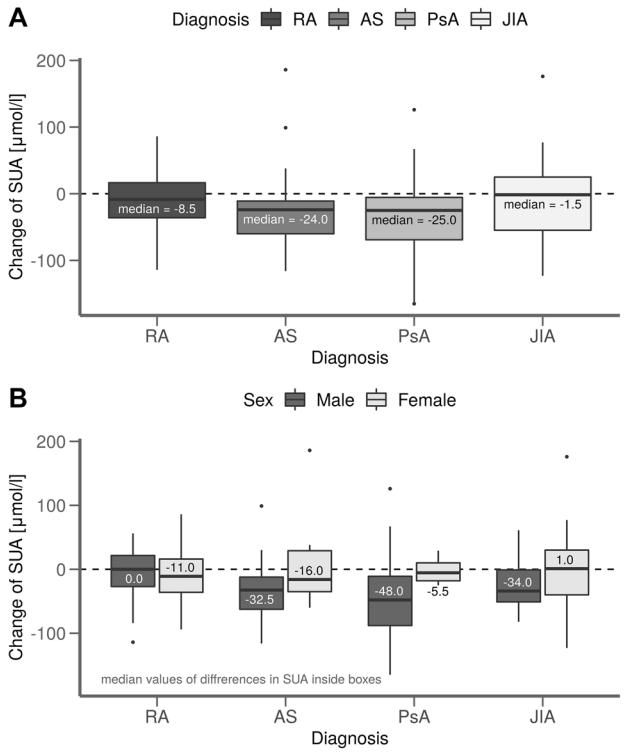

Fig. 1 Change of SUA (ΔSUA) according to sex and diagnosis before (SUA_{M0}) and after 3 months (SUA_{M3}) of therapy with TNFis. **a** ΔSUA by diagnosis. **b** ΔSUA by diagnosis and sex. Note: $\Delta SUA = SUA_{M0} - SUA_{M3}$; hence, a negative ΔSUA represents an increase in SUA level in response to TNFis therapy

SIR in male patients. We have not seen differences in ΔSUA according to age.

We have observed significant decrease of the levels of CRP, IL-6, IL-8, and MCP-1 after treatment with TNFi, which is consistent with the previous studies [28, 29]. TNFα is a crucial cytokine in the pathogenesis of immune-mediated inflammatory diseases including RA, PsA, JIA, AS, or inflammatory bowel diseases. TNFα can induce expression of other pro-inflammatory cytokines such as IL-1β, IL-6, or IL-8 [30]. Promotion of the inflammatory response by TNFα can occur directly by stimulating IL-1 secretion or by inducing other pro-inflammatory cytokines, such as IL-6, which contributes to the production of acute phase reactants [31]. It has been assumed that suppressing TNFα can block the entire inflammatory response [32]. However, in several studies, the cytokine profile after treatment with TNFi was heterogeneous (as in our study) and TNFα levels did not decrease in subjects treated with TNFi, despite clinical improvement [29, 33].

Our study has several limitations. First, we studied patients with different types of rheumatic inflammatory diseases as proxies for patients with gout. The chronic nature and autoimmune pathophysiology shared by these SARDs may differ from the acute flares characteristic of gout, as may the mechanisms underlying the coincident changes in SUA levels. Second, the difference in the use of NSAIDs before and after initiation of TNFis therapy may have confounded our results, particularly because NSAIDs are known to confer uricosuric effects [34]. However, when we analyzed the patient-reported use of NSAIDs, based on their clinical questionnaire responses, we could not detect a relationship between the use of NSAIDs and the ΔSUA, although underreporting still may have played a role. The use of glucocorticoids could also potentially affect SUA level [35, 36]. However, most of our patients had stable dose of glucocorticoids at baseline and after 3 months of anti-TNF treatment. After adjustment for sex, the use of glucocorticoids did not confer a statistically significant effect on the ΔSUA. Third, we did not evaluate the patients' dietary patterns in the present study. We can speculate that food intake decreases, or its composition changes during periods of active disease. Fasting has been shown to induce decreased SUA levels, despite the lack of significant body weight changes [37]. Finally, we did not analyze the intestinal excretion of uric acid, known to account for about one-third of urate excretion [38, 39], due to the invasive nature of the procedures required to collect this sample.

Our study has also several strengths. We studied a large cohort of patients with highly active SARDs starting first-line therapy with a single class of potent anti-inflammatory drugs with a targeted mechanism of action. We maintained a consistent time frame for sample collection, and measured large number of analytes, all of which have been implicated in inflammation-induced SUA fluctuations. In conclusion, we have shown that TNFi-induced abrogation of systemic inflammation in patients with several SARDs was associated with a significant increase in SUA. None of the measured pro-inflammatory cytokines appeared to be the driver of this observed change in SUA, nor the oxidization of SUA to allantoin to be the responsible mechanism. Further studies are needed to clarify the pathophysiology of lowering of SUA levels during an SIR.

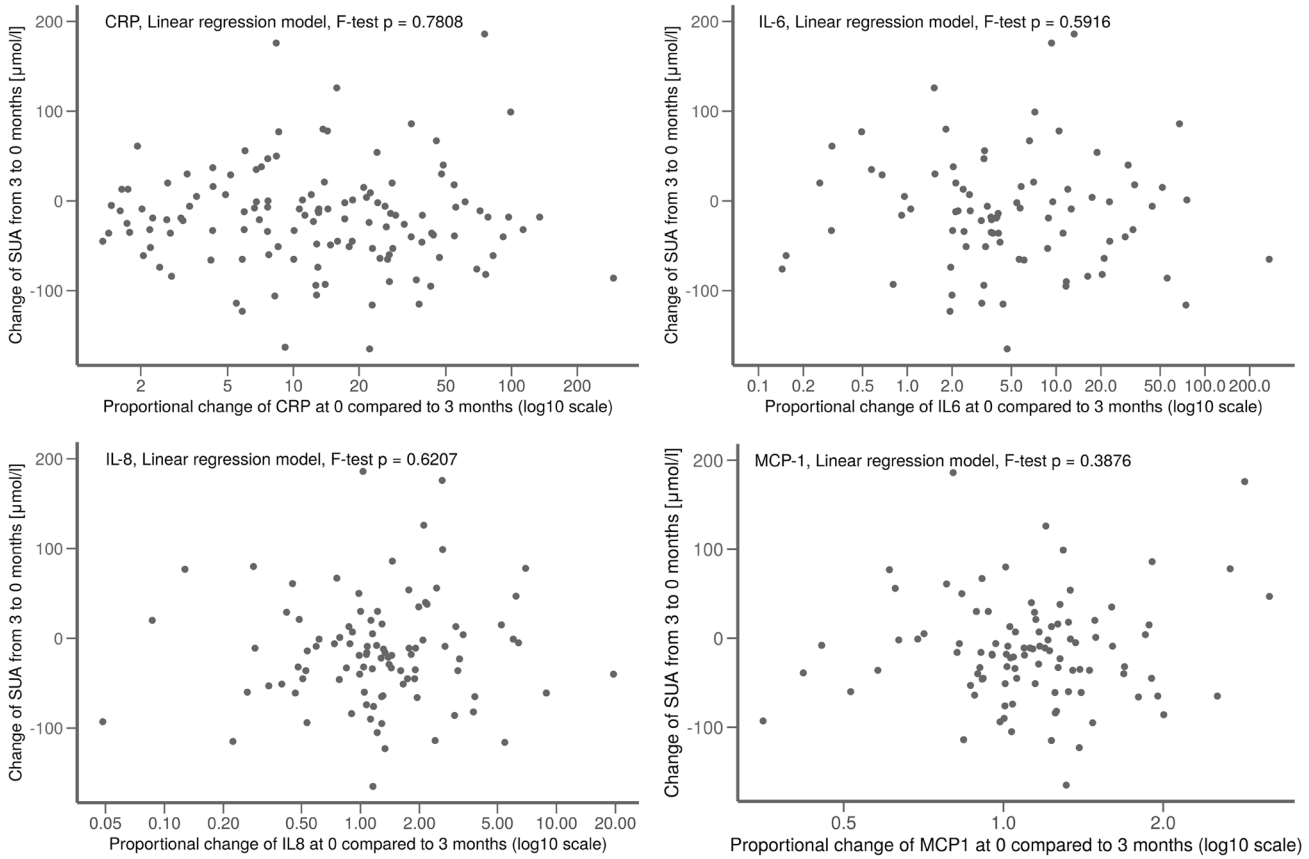

Fig. 2 Scatterplots of ΔSUA on (log-transformed) change in CRP and other selected pro-inflammatory cytokines with fitted regression lines

Acknowledgements We would like to thank Dr. Laszlo Wenchich and the members of the Department of Clinical Biochemistry and Hematology (Institute of Rheumatology) for their kind assistance with the biochemical measurements.

Author contributions All authors were involved in drafting the manuscript or revising it critically for content. LH planned and performed most of the measurements, conducted data analysis, and wrote the manuscript. MP conducted statistical data analysis and prepared the figures. HH and AM helped with measurements of cytokines and with analyzing data. PK and KK carried out mass spectrometric measurements. MH and BS provided scientific input and interpretation of data. JZ designed the project, supervised its conduct, and helped to write the manuscript. The final manuscript has been seen and approved by all authors.

Funding This work was supported by the Charles University Research Grant GA UK no. 940517, the Ministry of Health of the Czech Republic (Institute of Rheumatology—Conceptual Development of Research Organization, 00023728), and the Czech Science Foundation, Grant no. 19-18005Y. LH was a recipient of the ARTICULUM Fellowship.

Compliance with ethical standards

Conflict of interest All authors declare that there is no conflict of interest regarding the publication of this article.

Ethical approval All procedures in this study were in accordance with the ethical standards of the institutional and national research committee (Czech Multicentre Research Ethics Committee, no. 201611 S300 and Institutional Ethics Committee of Institute of Rheumatology, Prague, Czech Republic, no. 10113/2016) and with the 1964 Helsinki declaration and its later amendments.

References

1. Schlesinger N, Schumacher HR Jr, Beutler AM (1998) Serum uric acid in acute gout. Ann Rheum Dis 57(7):443–444
2. McCarty DJ (1994) Gout without hyperuricemia. JAMA 271(4):302–303. https://doi.org/10.1001/jama.1994.03510280064034
3. Logan JA, Morrison E, McGill PE (1997) Serum uric acid in acute gout. Ann Rheum Dis 56(11):696–697
4. Waldron JL, Ashby HL, Razavi C, Thomas OL, Chugh S, Deshpande S, Ford C, Gama R (2013) The effect of the systemic inflammatory response, as provoked by elective orthopaedic surgery, on serum uric acid in patients without gout: a prospective study. Rheumatology (Oxford, England) 52(4):676–678. https://doi.org/10.1093/rheumatology/kes327
5. Tsutani H, Yoshio N, Ueda T (2000) Interleukin 6 reduces serum urate concentrations. J Rheumatol 27(2):554

6. Urano W, Yamanaka H, Tsutani H, Nakajima H, Matsuda Y, Taniguchi A, Hara M, Kamatani N (2002) The inflammatory process in the mechanism of decreased serum uric acid concentrations during acute gouty arthritis. J Rheumatol 29(9):1950–1953
7. Ames BN, Cathcart R, Schwiers E, Hochstein P (1981) Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. Proc Natl Acad Sci USA 78(11):6858–6862
8. Becker BF (1993) Towards the physiological function of uric acid. Free Radic Biol Med 14(6):615–631
9. Re R, Pellegrini N, Proteggente A, Pannala A, Yang M, Rice-Evans C (1999) Antioxidant activity applying an improved ABTS radical cation decolorization assay. Free Radic Biol Med 26(9–10):1231–1237
10. Kellogg EW 3rd, Fridovich I (1977) Liposome oxidation and erythrocyte lysis by enzymically generated superoxide and hydrogen peroxide. J Biol Chem 252(19):6721–6728
11. Yeldandi AV, Patel YD, Liao M, Kao FT, Rao MS, Reddy JK, Le Beau MM (1992) Localization of the human urate oxidase gene (UOX) to 1p22. Cytogenet Cell Genet 61(2):121–122. https://doi.org/10.1159/000133386
12. Kaur H, Halliwell B (1990) Action of biologically-relevant oxidizing species upon uric acid. Identification of uric acid oxidation products. Chem Biol Interact 73(2–3):235–247
13. Hellsten Y, Svensson M, Sjodin B, Smith S, Christensen A, Richter EA, Bangsbo J (2001) Allantoin formation and urate and glutathione exchange in human muscle during submaximal exercise. Free Radic Biol Med 31(11):1313–1322
14. Kand'ar R, Zakova P, Muzakova V (2006) Monitoring of antioxidant properties of uric acid in humans for a consideration measuring of levels of allantoin in plasma by liquid chromatography. Clin Chim Acta 365(1–2):249–256. https://doi.org/10.1016/j.cca.2005.09.002
15. Marrocco I, Altieri F, Peluso I (2017) Measurement and clinical significance of biomarkers of oxidative stress in humans. Oxid Med Cell Longev 2017:6501046. https://doi.org/10.1155/2017/6501046
16. Grootveld M, Halliwell B (1987) Measurement of allantoin and uric acid in human body fluids. A potential index of free-radical reactions in vivo? Biochem J 243(3):803–808
17. Stamp LK, Turner R, Khalilova IS, Zhang M, Drake J, Forbes LV, Kettle AJ (2014) Myeloperoxidase and oxidation of uric acid in gout: implications for the clinical consequences of hyperuricaemia. Rheumatology 53(11):1958–1965. https://doi.org/10.1093/rheumatology/keu218
18. Lyngdoh T, Marques-Vidal P, Paccaud F, Preisig M, Waeber G, Bochud M, Vollenweider P (2011) Elevated serum uric acid is associated with high circulating inflammatory cytokines in the population-based Colaus study. PLoS One 6(5):e19901. https://doi.org/10.1371/journal.pone.0019901
19. Ruggiero C, Cherubini A, Ble A, Bos AJ, Maggio M, Dixit VD, Lauretani F, Bandinelli S, Senin U, Ferrucci L (2006) Uric acid and inflammatory markers. Eur Heart J 27(10):1174–1181. https://doi.org/10.1093/eurheartj/ehi879
20. Shi Y, Evans JE, Rock KL (2003) Molecular identification of a danger signal that alerts the immune system to dying cells. Nature 425(6957):516–521. https://doi.org/10.1038/nature01991
21. Braga TT, Forni MF, Correa-Costa M, Ramos RN, Barbuto JA, Branco P, Castoldi A, Hiyane MI, Davanso MR, Latz E, Franklin BS, Kowaltowski AJ, Camara NOS (2017) Soluble uric acid activates the NLRP3 inflammasome. Sci Rep 7:39884. https://doi.org/10.1038/srep39884
22. Busso N, So A (2010) Mechanisms of inflammation in gout. Arthritis Res Ther 12(2):206. https://doi.org/10.1186/ar2952
23. Torres R, Macdonald L, Croll SD, Reinhardt J, Dore A, Stevens S, Hylton DM, Rudge JS, Liu-Bryan R, Terkeltaub RA, Yancopoulos GD, Murphy AJ (2009) Hyperalgesia, synovitis and multiple biomarkers of inflammation are suppressed by interleukin 1 inhibition in a novel animal model of gouty arthritis. Ann Rheum Dis 68(10):1602–1608. https://doi.org/10.1136/ard.2009.109355
24. Lopera-Mesa TM, Mita-Mendoza NK, van de Hoef DL, Doumbia S, Konate D, Doumbouya M, Gu W, Traore K, Diakite SA, Remaley AT, Anderson JM, Rodriguez A, Fay MP, Long CA, Diakite M, Fairhurst RM (2012) Plasma uric acid levels correlate with inflammation and disease severity in Malian children with *Plasmodium falciparum* malaria. PLoS One 7(10):e46424. https://doi.org/10.1371/journal.pone.0046424
25. Panoulas VF, Milionis HJ, Douglas KMJ, Nightingale P, Kita MD, Klocke R, Elisaf MS, Kitas GD (2007) Association of serum uric acid with cardiovascular disease in rheumatoid arthritis. Rheumatology 46(9):1466–1470. https://doi.org/10.1093/rheumatology/kem159
26. Panoulas VF, Douglas KMJ, Milionis HJ, Nightingale P, Kita MD, Klocke R, Metsios GS, Stavropoulos-Kalinoglou A, Elisaf MS, Kitas GD (2007) Serum uric acid is independently associated with hypertension in patients with rheumatoid arthritis. J Hum Hypertens 22:177. https://doi.org/10.1038/sj.jhh.1002298
27. Ogihara H, Ogihara T, Miki M, Yasuda H, Mino M (1995) Plasma copper and antioxidant status in Wilson's disease. Pediatr Res 37(2):219–226. https://doi.org/10.1203/00006450-199502000-00016
28. Lembo S, Capasso R, Balato A, Cirillo T, Flora F, Zappia V, Balato N, Ingrosso D, Ayala F (2014) MCP-1 in psoriatic patients: effect of biological therapy. J Dermatol Treat 25(1):83–86. https://doi.org/10.3109/09546634.2013.782091
29. Walters HM, Pan N, Lehman TJ, Adams A, Kalliolias GD, Zhu YS, Santiago F, Nguyen J, Sitaras L, Cunningham-Rundles S, Walsh TJ, Toussi SS (2016) The impact of disease activity and tumour necrosis factor-α inhibitor therapy on cytokine levels in juvenile idiopathic arthritis. Clin Exp Immunol 184(3):308–317. https://doi.org/10.1111/cei.12782
30. Feldmann M, Maini SR (2008) Role of cytokines in rheumatoid arthritis: an education in pathophysiology and therapeutics. Immunol Rev 223:7–19. https://doi.org/10.1111/j.1600-065X.2008.00626.x
31. Calabrese LH, Rose-John S (2014) IL-6 biology: implications for clinical targeting in rheumatic disease. Nat Rev Rheumatol 10(12):720–727. https://doi.org/10.1038/nrrheum.2014.127
32. Ware CF (2005) Network communications: lymphotoxins, LIGHT, and TNF. Annu Rev Immunol 23:787–819. https://doi.org/10.1146/annurev.immunol.23.021704.115719
33. Schulz M, Dotzlaw H, Neeck G (2014) Ankylosing spondylitis and rheumatoid arthritis: serum levels of TNF-alpha and Its soluble receptors during the course of therapy with etanercept and infliximab. Biomed Res Int 2014:675108. https://doi.org/10.1155/2014/675108
34. Daskalopoulou SS, Tzovaras V, Mikhailidis DP, Elisaf M (2005) Effect on serum uric acid levels of drugs prescribed for indications other than treating hyperuricaemia. Curr Pharm Des 11(32):4161–4175
35. Schlesinger N (2014) Treatment of acute gout. Rheum Dis Clin N Am 40(2):329–341. https://doi.org/10.1016/j.rdc.2014.01.008
36. Riccardi C, Bruscoli S, Migliorati G (2002) Molecular mechanisms of immunomodulatory activity of glucocorticoids. Pharmacol Res 45(5):361–368
37. Akanji AO, Mojiminiyi OA, Abdella N (2000) Beneficial changes in serum apo A-1 and its ratio to apo B and HDL in stable hyperlipidaemic subjects after Ramadan fasting in Kuwait. Eur J Clin Nutr 54(6):508–513

38. Sorensen LB (1965) Role of the intestinal tract in the elimination of uric acid. Arthritis Rheumatol 8(5):694–706
39. Abramson RG, Levitt MF (1976) Use of pyrazinamide to assess renal uric acid transport in the rat: a micropuncture study. Am J Physiol 230(5):1276–1283. https://doi.org/10.1152/ajplegacy.1976.230.5.1276