Prednisone in Uric Acid Lowering in Symptomatic Heart Failure Patients with Hyperuricemia — The PUSH-PATH3 Study

Hong Meng, Gang Liu, Jianlong Zhai, Yuzhi Zhen, Qingzhen Zhao, Mingqi Zheng, Guoping Ma, Le Wang, Li Tian, Lishuang Ji, Linan Duan, Lizhuo Li, Kunshen Liu, and Chao Liu

ABSTRACT. ***Objective.*** To determine the safety and efficacy of prednisone in patients with symptomatic heart failure (HF) and hyperuricemia.

Methods. Prednisone therapy was administered for a short time to 191 symptomatic HF patients with hyperuricemia (serum uric acid > 7 mg/dl).

Results. Prednisone significantly reduced serum uric acid by 2.99 mg/dl ($p < 0.01$) and serum creatinine by 0.17 mg/dl ($p < 0.01$). These favorable effects were associated with a remarkable increase in urine output, improvement in renal function, and improvement in clinical status.

Conclusion. Prednisone can be used safely in symptomatic HF patients with hyperuricemia. (J Rheumatol First Release March 15 2015; doi:10.3899/jrheum.141037)

Key Indexing Terms:
HEART FAILURE HYPERURICEMIA PREDNISONE RENAL FUNCTION

Growing evidence shows that inflammatory activation is an important pathway in disease progression in heart failure (HF), and raised plasma levels of cytokines predict worse prognosis in patients with HF[1]. Inflammatory activation also plays an important role in cardiorenal syndrome[1]. Tubulointerstitial inflammation and oxidative stress enhance local angiotensin II generation and compromise dopamine D1 receptor, leading to proximal and distal tubule sodium reabsorption[2]. Uric acid is a marker of impaired renal function in HF[3,4]. Therefore, patients with HF frequently present with hyperuricemia. Moreover, gout, as an inflammatory disease, is not uncommon in this population. But chronic drug interaction between HF therapy and pharmacological agents used for hyperuricemia and gout is a challenging problem[5].

We found that prednisone, a commonly used antiinflammatory agent, could not only lower serum uric acid (SUA) but also improve renal responsiveness to diuretics in patients with HF, in a randomized clinical trial[6] with a small sample. To further determine its safety and efficacy when used in the short term (< 2 weeks), we retrospectively reviewed data from 191 symptomatic HF patients with hyperuricemia treated with prednisone and assessed its effects in SUA lowering and renal function improvement.

From the Heart Center, The First Hospital of Hebei Medical University, Shijiazhuang, China.

Supported by Hebei Province Government (Hebei Provincial Major Medical Research Project ZD2013083).

H. Meng, MD; G. Liu, MD, J. Zhai, MD; Y. Zhen, MD; Q. Zhao, MD; M. Zheng, MD; G. Ma, MD; L. Wang, MD; L. Tian, MD; L. Ji, MD; L. Duan, MD; L. Li, MD; K. Liu, MD; C. Liu, MD, The First Hospital of Hebei Medical University.

Address correspondence to Dr. C. Liu, Heart Center, The First Hospital of Hebei Medical University, 89 Donggang Road, Shijiazhuang, Hebei Province, China 050031. E-mail: dr.liuchao@gmail.com; or Dr. K. Liu, e-mail: ksliud@sohu.com

Accepted for publication January 14, 2015.

MATERIALS AND METHODS

Patients. Our hospital committee on medical research ethics approved the study protocol. This study complied with the Declaration of Helsinki. Inclusion criteria were adult symptomatic HF patients with New York Heart Association function Class III-IV, fasting SUA > 7.0 mg/dl. Patients with active myocarditis and patients who were taking xanthine oxidase inhibitors were excluded. From January 2010 to November 2013, 191 symptomatic HF patients with hyperuricemia were enrolled. Table 1 lists the demographic characteristics of the patients at baseline.

Methods. Patients were treated with prednisone as bridge therapy between decompensated HF to compensated HF because prednisone can improve renal function and renal responsiveness to diuretic therapy[6,7,8,9,10]. The dose of prednisone was based on clinical status judged by caregiving physicians, and median dose was 50 mg/day (interquartile range 30 mg–60 mg). Daily urine output was recorded. Concentrations of SUA and serum creatinine (SCr) were recorded at baseline, timepoint 1 (5th to 7th day after treatment initiation), and timepoint 2 (10th to 14th day after treatment initiation).

Statistical analysis. Continuous variables are expressed as mean ± SD, unless stated otherwise. We used 1-way repeated measures ANOVA to test the treatment effects. Paired t-test was used to analyze differences in variables before and after treatment. Mixed linear models for repeated measures data with time varying covariate was used to determine the correlation of SCr and SUA. All statistical tests were performed with 2-sided alternatives and with a type I error of 0.05 and the use of SPSS software (version 16.0).

RESULTS

Effect of prednisone on SUA levels. Prednisone was given to 191 symptomatic HF patients with hyperuricemia. At

Table 1. Clinical characteristics of 191 patients with symptomatic HF and hyperuricemia. Data are expressed as mean ± SD or n (%).

Variables	Value
Age, yrs	52.1 ± 16.1
Male	149 (78.0)
HTN	32 (16.8)
AF	49 (25.7)
DM	30 (15.7)
Etiology of HF	
CAD	34 (17.8)
IDC	132 (69.1)
VHD	16 (8.4)
Others	9 (4.7)
NYHA functional class	
III	28 (15.7)
IV	163 (85.3)
LVEF ≥ 45%	34 (17.8)
Laboratory test	
SUA, mg/dl	10.39 ± 2.51
SCr, mg/dl	1.17 ± 0.38
Medication	
Furosemide	179 (93.7)
HCTZ	110 (57.6)
Spironolactone	159 (83.2)
Digitalis	76 (39.8)
ACE I	118 (61.8)
ARB	14 (7.3)
β-blocker	148 (77.5)

HTN: hypertension; AF: atrial fibrillation/flutter; DM: diabetes mellitus; CAD: coronary artery disease; IDC: idiopathic dilated cardiomyopathy; VHD: valvular heart disease; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; SUA: serum uric acid; SCr: serum creatinine; HCTZ: hydrochlorothiazide; ACE I: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers.

timepoint 1, SUA was measured for 165 patients, and at timepoint 2, for 168 patients. Only 3 patients did not have data at either timepoint 1 or timepoint 2, because of 2 early deaths and 1 patient lost to followup. Prednisone reduced SUA concentration in symptomatic HF patients with hyperuricemia by 1.69 mg/dl at timepoint 1 and 2.99 mg/dl at timepoint 2 compared with baseline (Table 2).

Effect of prednisone on renal function. It is noteworthy that the reduction of SUA was accompanied by dramatic SCr reduction (Table 2). Consistent with a previous finding, there was a clear correlation between SCr and SUA (Figure 1A). Adding prednisone to standard HF treatment did not cause fluid retention, and the hematocrit was increased from 36.5 ± 8.3% to 38.5 ± 7.9% after prednisone initiation (n = 47). Rather, it induced a slow but more potent diuresis (Figure 1B) without increasing the dose of furosemide (41.6 ± 33.5 mg/day at baseline compared with 37.7 ± 29.1 mg/day at the last time when the SUA was recorded).

Safety and tolerability. There were 8 deaths (4.2%) within 30 days in patients with symptomatic HF and hyperuricemia. Clinical status was improved in 172 patients (90%), remained unchanged in 4 patients (2.1%), and deteriorated in 7 patients (3.7%). Twenty-one out of 165 patients (12.7%) at timepoint 1 and 10 out of 168 patients (6.0%) at timepoint 2 had transient hypokalemia. All patients with diabetes mellitus had transient severe hyperglycemia, but it subsided when doses of insulin were adjusted. There was no acute gout attack recorded during prednisone treatment. Overall, prednisone was well tolerated in the symptomatic HF patients with hyperuricemia.

DISCUSSION

Prednisone resulted in a striking SUA reduction, as well as a significant improvement in renal function in the symptomatic HF patients with hyperuricemia. These favorable effects induced by prednisone were accompanied by a dramatic increase in urine output and an improvement in clinical status. We used prednisone as an add-on therapy. Therefore, our data did not support the use of glucocorticoids (GC) in lieu of diuretics.

Uric acid is the final product of purine degradation with xanthine oxidase, an enzyme implicated as a mechanistic participant in oxidant stress. About 70% of the uric acid is excreted through the kidneys and 30% through the gastrointestinal tract[11]. Hyperuricemia results from either overproduction or reduced excretion of uric acid, or both. In decompensated HF, glomerular filtration and tubular excretion of UA are impaired as a result of venous congestion[3,12]. The level of SCr reduction was well correlated with the level of SUA, indicating renal function improvement contributed much to SUA lowering in HF. Additionally, gout is a common comorbidity in patients with HF[5]. However,

Table 2. The effects of prednisone on SUA level and clinical improvement.

	Baseline, n = 191	Timepoint 1, n = 165	CFB at Timepoint 1, n = 165	Timepoint 2, n = 168	CFB at Timepoint 2, n = 168
SUA, mg/dl	10.39 ± 2.51	8.50 ± 2.44*	–1.69 ± 2.43#	7.48 ± 2.41*	–2.99 ± 2.73#
SCr, mg/dl	1.17 ± 0.38	1.06 ± 0.39*	–0.08 ± 0.31#	1.01 ± 0.35*	–0.17 ± 0.26#
Serum potassium, mmol/l	4.15 ± 0.70	4.21 ± 0.73	–0.07 ± 0.95	4.21 ± 0.57	–0.08 ± 0.87
Serum sodium, mmol/l	135.03 ± 5.51	135.52 ± 4.87	–0.77 ± 4.83	135.42 ± 5.35	0.07 ± 6.16
NYHA functional class	3.85 ± 0.35	3.06 ± 0.58*	–0.80 ± 0.50#	2.53 ± 0.70*	–1.33 ± 0.71#
Body weight, kg	71.02 ± 14.76	68.75 ± 13.56*	–2.27 ± 3.88#	67.88 ± 12.82*	–3.30 ± 4.46#

* $p < 0.01$ compared with baseline; # $p < 0.01$. SUA: serum uric acid; CFB: change from baseline; SCr: serum creatinine; NYHA: New York Heart Association.

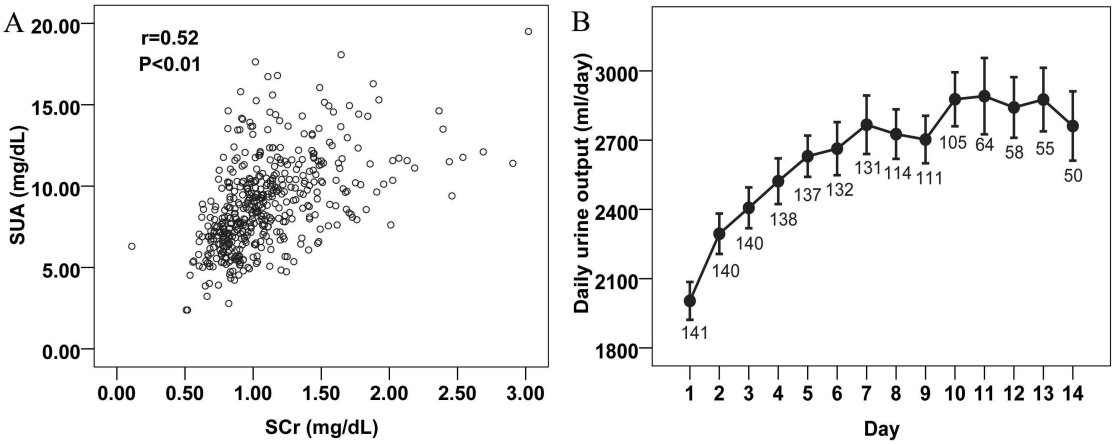

Figure 1. Correlation between SUA and SCr, and potentiating diuretic effect of prednisone on symptomatic HF patients with hyperuricemia. A. Correlation between SUA and SCr (Pearson correlation); SUA = 3.03 + 5.60*SCr (Equation obtained by mixed linear models with time varying covariate; intercept, $p < 0.01$; SCr, $p < 0.01$). B. Effect of prednisone on daily urine output; annotations below the markers are no. patients who had urine output recorded. Data in panel B were expressed as mean and standard error.

drug options are restricted. HF therapy and pharmacological agents used for gout exclude nonsteroidal antiinflammatory drugs because of their nephrotoxicity. Therefore, a drug that can lower UA and treat gouty arthritis as well as induce potent diuresis will be ideal in this setting.

It is noteworthy that renal-protective effects induced by prednisone were accompanied by a potent diuresis in symptomatic patients with systolic HF. Coupled with the newly emerging evidence that oral prednisolone and naproxen are equally effective in the initial treatment of gouty arthritis[13], prednisone might be the drug of choice for HF patients with hyperuricemia or gouty arthritis.

The role of GC in HF has changed. Using corticosteroids to treat HF was first reported in the 1950s[7]. With the advent of a potent diuretic such as furosemide, intractable cardiac edema became less intractable and GC vanished from the treatment of HF[7,8]. However, data show that GC can successfully overcome diuretic resistance in the patients who fail to respond to loop or combined diuretic therapy[7,14]. We demonstrated that GC could improve renal responsiveness to atrial natriuretic peptide by upregulating natriuretic peptide receptor-A expression in the inner medullary collecting duct cells both *in vivo* and *in vitro*, and produce a potent diuretic action in decompensated HF[15]. Moreover, there is evidence demonstrating that GC can dilate renal vasculature and increase renal plasma flow and glomerular filtration rate, a process that involves multiple pathways such as increased renal prostaglandin, nitric oxide, and dopamine production[7,8].

Inflammation and cardiorenal interaction in HF. In HF, several proinflammatory cytokines in response to neurohormones and sympathetic activation can be detected at high levels in the tissues and blood[1]. Inflammatory response, in turn, may further worsen the activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system, and cause renal injury[1]. Therefore, the antiinflammatory role of the glucocorticoid in attenuating diuretic resistance in HF cannot be excluded and merits further investigation.

The safety of corticosteroid treatment in patients is a major concern. Longterm or short-term corticosteroid use poses a high cardiovascular risk in the general population. However, HF patients with hyperuricemia have a 2-year mortality rate of about 40%[16,17]. For such a high-risk population, prednisone might have a role in improving their longterm survival[8].

Study limitations. The major limitation of our study was an inability to exclude contribution of placebo effects because of the lack of a control group. Second, the effect of prednisone on longterm mortality was also not evaluated. Third, there is still much to be done before this experimental approach to treat HF could become a common practice; efficacy and safety must be established. A dose-comparison study to determine the optimal dose of prednisone is needed, as are large-scale randomized controlled trials to establish its efficacy and safety. Fourth, the mechanism of UA-lowering effect induced by prednisone is speculative[18]. Preliminary data suggest corticosteroids might increase renal UA excretion[6,19]. But this hypothesis is to be examined in a current ongoing trial. Finally, the urate-lowering effect induced by prednisone might, theoretically, trigger acute flares. However, as a potent antiinflammatory agent, systematic prednisone administration is recommended by international guidelines to prevent acute gout flares when initiating urate-lowering therapy in patients with chronic gout[20]. Whether prednisone could trigger acute gout flare still needs further investigation in patients with symptomatic HF.

Prednisone can be safely used by symptomatic HF patients with hyperuricemia or acute gouty arthritis in the short term without worsening HF. Further large randomized controlled trials are warranted to corroborate these results.

REFERENCES

1. Colombo PC, Ganda A, Lin J, Onat D, Harxhi A, Iyasere JE, et al. Inflammatory activation: cardiac, renal, and cardio-renal interactions in patients with the cardiorenal syndrome. Heart Fail Rev 2012;17:177-90.
2. Rodriguez-Iturbe B, Franco M, Tapia E, Quiroz Y, Johnson RJ. Renal inflammation, autoimmunity and salt-sensitive hypertension. Clin Exp Pharmacol Physiol 2012;39:96-103.
3. Tian Y, Chen Y, Deng B, Liu G, Ji ZG, Zhao QZ, et al. Serum uric acid as an index of impaired renal function in congestive heart failure. J Geriatr Cardiol 2012;9:137-42.
4. Anker SD, Doehner W, Rauchhaus M, Sharma R, Francis D, Knosalla C, et al. Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. Circulation 2003;107:1991-7.
5. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J 2008;29:2388-442.
6. Liu C, Zhao Q, Zhen Y, Gao Y, Tian L, Wang L, et al. Prednisone in Uric Acid lowering in Symptomatic Heart Failure Patients With Hyperuricemia (PUSH-PATH) study. Can J Cardiol 2013; 29:1048-54.
7. Liu C, Liu K. Effects of glucocorticoids in potentiating diuresis in heart failure patients with diuretic resistance. J Card Fail 2014;20:625-9.
8. Liu C, Wang N, Meng H, Qiao M. Glucocorticoids for decompensated heart failure. Cochrane Database Syst Rev 2014; in press.
9. Liu C, Liu K, Group C-AS. Cardiac Outcome Prevention Effectiveness of Glucocorticoids in Acute Decompensated Heart Failure: COPE-ADHF Study. J Cardiovasc Pharmacol 2014; 63:333-8.
10. Liu C, Chen H, Zhou C, Ji Z, Liu G, Gao Y, et al. Potent potentiating diuretic effects of prednisone in congestive heart failure. J Cardiovasc Pharmacol 2006;48:173-6.
11. Sorensen LB, Levinson DJ. Origin and extrarenal elimination of uric acid in man. Nephron 1975;14:7-20.
12. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol 2009;53:589-96.
13. Janssens HJ, Janssen M, van de Lisdonk EH, van Riel PL, van Weel C. Use of oral prednisolone or naproxen for the treatment of gout arthritis: a double-blind, randomised equivalence trial. Lancet 2008;371:1854-60.
14. Liu C, Liu G, Zhou C, Ji Z, Zhen Y, Liu K. Potent diuretic effects of prednisone in heart failure patients with refractory diuretic resistance. Can J Cardiol 2007;23:865-8.
15. Liu C, Chen Y, Kang Y, Ni Z, Xiu H, Guan J, et al. Glucocorticoids improve renal responsiveness to atrial natriuretic peptide by up-regulating natriuretic peptide receptor-A expression in the renal inner medullary collecting duct in decompensated heart failure. J Pharmacol Exp Ther 2011;339:203-9.
16. Malek F, Ostadal P, Parenica J, Jarkovsky J, Vitovec J, Widimsky P, et al. Uric acid, allopurinol therapy, and mortality in patients with acute heart failure—results of the Acute HEart FAilure Database registry. J Crit Care 2012;27:737 e11-24.
17. Wu AH, Ghali JK, Neuberg GW, O'Connor CM, Carson PE, Levy WC. Uric acid level and allopurinol use as risk markers of mortality and morbidity in systolic heart failure. Am Heart J 2010;160:928-33.
18. Liu C, Liu K. Reply to Day et al.—hypouricemic effect of prednisone in heart failure: possible mechanisms. Can J Cardiol 2014;30:376 e3.
19. Maly J, Nadvornikova H, Schuck O. The effect of prednisone and azathioprine (Imuran) on renal excretion of uric acid. Int J Clin Pharmacol Ther Toxicol 1982;20:44-6.
20. Khanna D, Khanna PP, Fitzgerald JD, Singh MK, Bae S, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res 2012;64:1447-61.