

Is rasburicase an effective alternative to allopurinol for management of hyperuricemia in renal failure patients?

A double blind-randomized study

S. DE ANGELIS, A. NOCE, L. DI RENZO*, R. CIANCI*§, A. NATICCHIA, G.F. GIARRIZZO*, F. GIORDANO**, C. TOZZO, G. SPLENDIANI, A. DE LORENZO*

Division of Nephrology, University "Tor Vergata" – Rome (Italy)

*Department of Neuroscience, Division of Human Nutrition, University of "Tor Vergata" – Rome (Italy)

**Division of Nephrology, Nuova I.T.O.R. – Rome (Italy)

§Institute of Internal Medicine, Catholic University – Rome (Italy)

Abstract. – Recent epidemiological studies provide a clear evidence that hyperuricemia is associated with hypertension, coronary heart disease, left ventricular hypertrophy and progression of renal disease. Aim of our study was to assess the effect of low dosage of recombinant urate oxidase on hyperuricemia in renal failure patients that already receiving allopurinol. Our study group consisted of 43 renal failure patients, 23 women and 20 men. The mean age was 74 years (range 36-90 years). The following variables were studied on admission: serum creatinine, blood urea nitrogen and serum uric acid. Intravenous rasburicase was administered at a dose of 0.02 mg/kg/day on 3 consecutive days in patients with serum uric acid between 8-10 mg/dl, on 5 consecutive days in patients with serum uric acid between 10-15 mg/dl and on 7 consecutive days in patients with serum uric acid > 15 mg/dl. Uric acid levels were assayed after 48 hours and 7 days after rasburicase treatment. Mean values of uric acid levels after 48 hours were 2.47 mg/dl (\pm 1.58) in men and 2.77 mg/dl (\pm 2.24) in woman, where'as mean values of uric acid levels after 7 days were 4.45 mg/dl (\pm 2.0) in men and 5.75 mg/dl (\pm 1.9) in woman. No significant relationship were found between uric acid and creatinine as before as well after therapy. There were no side effects in all patients included in the study. After 7 days, the rasburicase therapy showed more antihyperuricemic effect in men (59%) than in women (46%).

Key Words:

Hyperuricemia, Chronic renal failure, Allopurinol, Recombinant urate oxidase.

Introduction

Hyperuricemia is defined as a serum uric acid (SUA) concentration exceeding the limit of solubility, about 6.8 mg/dL (400 mmol/L). In patients with renal disease uric acid urinary excretion is usually decreased and whether this will give rise to hyperuricemia depends only on the gastrointestinal excretory compensation¹.

Recent studies provide a clear evidence that hyperuricemia is associated with essential hypertension, coronary heart disease, left ventricular hypertrophy and progression of renal disease².

The role of uric acid in the progression of renal disease has been investigated by Kang et al in normal rats using a model of mild hyperuricemia induced by the uricase inhibitor, oxonic acid (OA)³. The major novel finding of this study was that modest hyperuricemia markedly exacerbated renal progression through activation of the renin angiotensin system (RAS) and vascular smooth muscle cell (VSMC) proliferation via COX-2 pathway. In this remnant kidney model of progressive renal disease uric acid behave an independent risk factor for renal progression, since hyperuricemia increased systemic blood pressure, renal afferent arteriopathy, increased glomerular hydrostatic pressure, proteinuria and progressive renal scarring.

The relationship between hyperuricemia and progression of renal disease in humans has been confirmed from the study of Iseki et al who examined the significance of hyperuricemia on the

early detection of renal failure in a cohort of screened subjects⁴. Therefore SUA should be acknowledged as a significant modifiable risk factor and a potential target for treatment, but we do not as yet have conclusive human clinical trial data to prove the utility of uric acid-lowering regimens as agents to attenuate progressive renal injury⁵.

Usually, the average dose of allopurinol (300 mg per day) in patients with chronic kidney disease, if correctly titrated to serum creatinine levels, resulted often inadequate to decrease SUA < 7.60 mg/dL. Moreover, the side effects of allopurinol may vary by a simple urticarial skin rash to a life-threatening toxicity that is characterized by a diffuse desquamative skin rash, fever, hepatic dysfunction, eosinophilia and worsening renal function. About eighty percent of the patients reported to have this syndrome had pre-existing renal failure, obviously followed by a promptly drug withdrawal⁶.

Intravenous recombinant urate oxidase (Rasburicase) is considered an effective alternative to oral allopurinol for management of hyperuricemia⁷. Advantages over allopurinol include a more rapid onset and superior uric acid-lowering activity. Disadvantages of rasburicase are its propensity for severe hypersensitivity reactions and hemolytic anemia, although the risk of these complications appears relatively low. At the moment the rasburicase is used only for tumor lysis syndrome prevention in cancer patients (primarily lymphoma or leukemia) at the dosage of 0.20 mg/kg.

Since hyperuricemia should have treated with any uric acid lowering agent in order to improve morbidity and mortality in renal patients, we thought to investigate the effects of Rasburicase in patients with renal insufficiency at the dosage of 0.02 mg/kg/day, that is very lower than dosage that's usually used for tumor lysis syndrome prevention (0.20 mg/kg).

Materials and Methods

Study Design

The Rasburicase versus Allopurinol Controlled Trial, a phase 3, randomized, double-blind, 2 week, multicenter trial, compared the safety and efficacy of Rasburicase with the safety and efficacy of Allopurinol in adult subjects with the following inclusion criteria:

- presence of renal disease and serum creatinine level greater 1.4 mg/dL
- stable clinical conditions in terms of general health and renal function
- serum uric acid levels steadily over 7.6 mg/dL

We excluded either patients with glucose-6-phosphate dehydrogenase deficiency, because the usage of rasburicase in these subjects can cause hemolysis, or those with a history of atopy.

We conducted the study between June 2005 and June 2006 at the Division of Nephrology of University Tor Vergata and Division of Nephrology of "Nuova ITOR Hospital, in Rome, Italy. A computer-generated central randomization schedule was used to assign each subject to one of two groups: Rasburicase at 0.02 mg/kg per day or Allopurinol at 300 mg per day.

Subjects already receiving urate-lowering therapy underwent a one week washout period before undergoing randomization. Approval was obtained from Institutional Ethics Committee and carried out in patients that were followed up. All subjects gave written informed consent before enrollement.

Patients

Patients were randomly assigned in a 1:1 ratio to receive either rasburicase or allopurinol treatment, in a double-blind fashion by means of central, computerized system of randomisation.

A total of 39 renal failure patients were enrolled in the rasburicase group, 19 women and 20 men. The mean age of patients was 76 years (range 36-90 years).

The following variables were studied on admission: serum creatinine 4.5 mg/dL (SD 2.2), blood urea nitrogen 167.2 mg/dL (SD 80.4) and serum uric acid 10.7 mg/dL (SD 2.1).

30 patients (77 %) had previously taken allopurinol, that was withdrawn temporarily since 1 week before the start of the study and was restarted at once at the end of the study, that is 1 week after the last rasburicase administration. The remaining 9 (23%) had a history of allopurinol-related adverse event. According to distribution in general population, prevalence of metabolic syndrome and association with hyperuricemia were about 12% of patients enrolled in the study.

The dose of rasburicase (0.02 mg/kg/day) was administered according to serum acid level:

- on 3 consecutive days in patients with serum uric acid between 8-10 mg/dl

- on 5 consecutive days in patients with serum uric acid between 10-15 mg/dl
- on 7 consecutive days in patients with serum uric acid > 15 mg/dl

A total of 41 patients were enrolled in the Allopurinol group, 15 women and 26 men. The mean age of patients was 66 years (range 35-90 years). Following variables were studied on admission: serum creatinine 2.7 mg/dL (SD 1.8), blood urea nitrogen 99.0 mg/dL (SD 55.3) and serum uric Acid 7.6 mg/dL (SD 1.3).

All patients had previously taken allopurinol, at the dosage that was adjusted according to baseline renal function. Dosage of the other drugs were continued in both groups, according to the individual patient's clinical conditions.

Adverse Event

A treatment-emergent adverse event was defined as an adverse event occurring during the period between the first dose and 7 days after the final dose of the study drug.

Any adverse event, either minor or severe, that has been considered to be undoubtedly related to the use of rasburicase or allopurinol, was recorded during the follow-up assessment.

Outcome Analysis

According to Iseki et al⁴, we previously established that the cut-off value for serum uric acid on the future development of End Syndrome Renal Disease (ESRD) should be 5.5 mg/dL (327 µmol/L), both in men and women.

Uric acid levels were assayed after 48 hours and 7 days after rasburicase treatment, whereas in control group patients at the start and 7 days after the first assessment.

End Points

The primary efficacy end point was serum uric acid reduction less than 5.5 mg/dL at first programmed measurement, after 48 hour. The secondary efficacy end point included the proportion of subjects with serum urate levels of less than 5.5 mg/dL at the second programmed measurement, that is 7 days after the last rasburicase administration.

Statistical Analysis

Statistical analysis was performed using SPSS statistical package (SPSS Chicago, IL, version 5.0 for Windows). Descriptive values were expressed as mean value (standard deviation, SD), *p* value of < 0.05 was considered statistically significant. Differences between variables were assessed using appropriate statistical test based on the underlying distribution of the variables by two-away ANOVA followed by correction for multiple comparison (Bonferroni test) and Chi-Square test. To study the linear relationship among parameters was assessed by linear regression and Pearson's correlation analysis.

Results

Males and females have showed (Table I), a significant statistical differences by ANOVA of serum creatinine (*p* = 0.01). Conversely, according to the gender serum uric acid did not show any statistical difference. Additionally (Figure 1), there was observed a significant decrease by Bonferroni test (*p* < 0.001) of serum uric acid during Rasburicase administration in all patients:

Table I. Clinical characteristics at baseline (19 females and 20 males).

	Males (n = 20)		Females (n = 19)		Significance (<i>p</i>) ANOVA-test analysis
	Mean	SD	Mean	SD	
Age (yrs)	76.40	7.45	75.63	13.35	NS
SUA (mg/dL)	10.92	1.76	10.46	2.41	NS
SC (mg/dL)	5.31	2.29	3.58	1.62	0.01
Azotemia (mg/dL)	152.89	83.94	180.85	82.64	NS
SBP (mmHg)	133.00	22.03	126.61	16.35	NS
DBP (mmHg)	76.00	8.82	71.05	7.38	NS

SUA = Serum Uric Acid; SC = Serum Creatinine; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; NS = Not Significant.

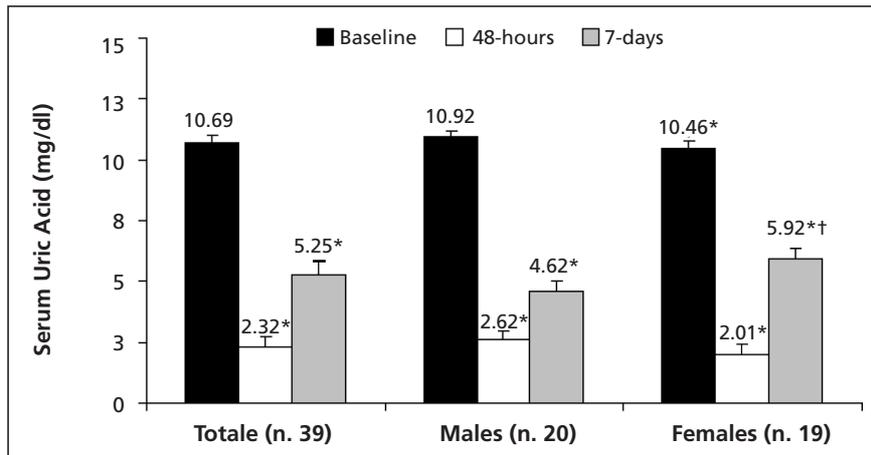


Figure 1. Rasburicase administration and serum uric levels. Differences between pairs of means by a post hoc Tukey and Bonferroni testes. * $p < 0.001$ Baseline vs 48-hours and 7-days, † $p = 0.038$ Males vs Females.

- from 10.69 mg/dL (± 2.09) at baseline [10.92 mg/dL (± 1.76) in males and 10.46 mg/dL (± 2.41) in females] to 2.32 mg/dL (± 1.61) after 48 hours [2.62 mg/dL (± 1.53) in males and 2.01 mg/dL (± 1.68) in females];
- from 10.69 mg/dL to 5.25 after 7 days [4.61 mg/dL (± 1.91) in males and 5.92 mg/dL (± 1.86) in females].

Moreover after 7 days was observed a significant increase ($p = 0.038$) of the serum uric acid in females compared with males.

According to a cut-off value for serum uric acid of 5.5 mg/dL (327 mmol/L), a reduction of percentage of patients with excess of UA (> 5.5 mg/dL) were observed:

- from 100% at baseline to 8% after 48 hours;
- from 100% at baseline to 53 % after 7 days; (Chi-Square = 66.86, $p < 0.001$) (Figure 2).

No significant relationship were found between SUA levels and creatinine as before as well after rasburicase therapy (Figure 3), meaning the independence of hyperuricemia as regards the renal failure .

There were no side effects in all patients included in the study.

At the last, after 7 days, the Rasburicase therapy showed more antihyperuricemic effect compared to Allopurinol treatment (Figure 4).

Discussion

Up to date, pharmacologic urate lowering strategies involve either reducing urate production with xanthine-oxidase inhibitor or enhancing urinary excretion of uric acid with uricosuric agent. The xanthine-oxidase inhibitor allopurinol is the most

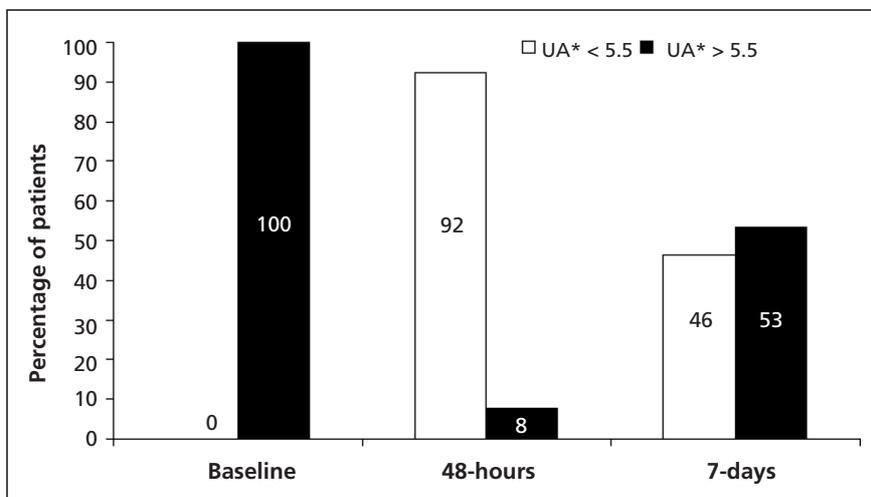
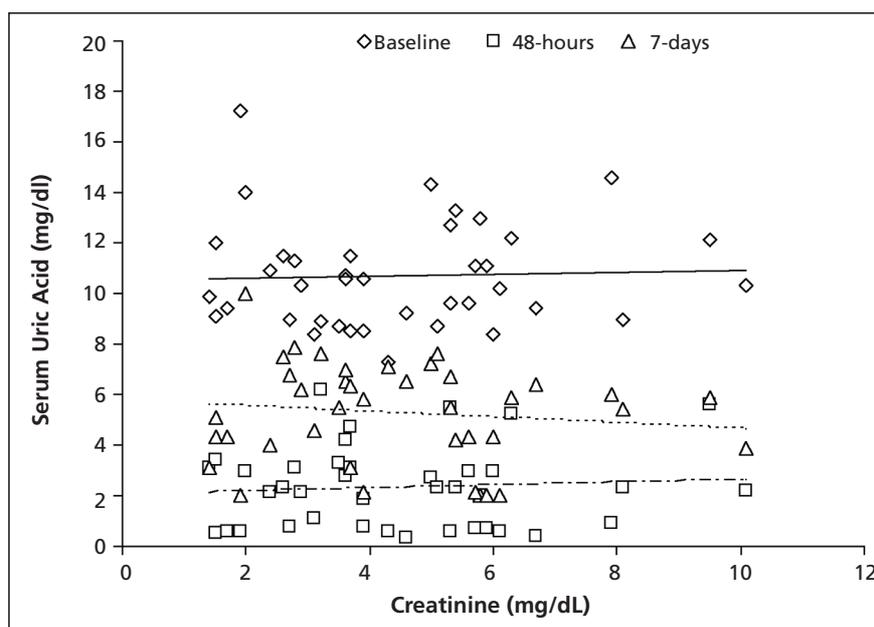


Figure 2. Rasburicase administration and hyperuricemia. Percentage of patients with and without hyperuricemia. *UA = serum uric acid levels. (Chi-Square = 66.85, $p < 0.001$).

Figure 3. Rasburicase administration and creatinine levels. Linear regression between creatinine and serum uric acid.

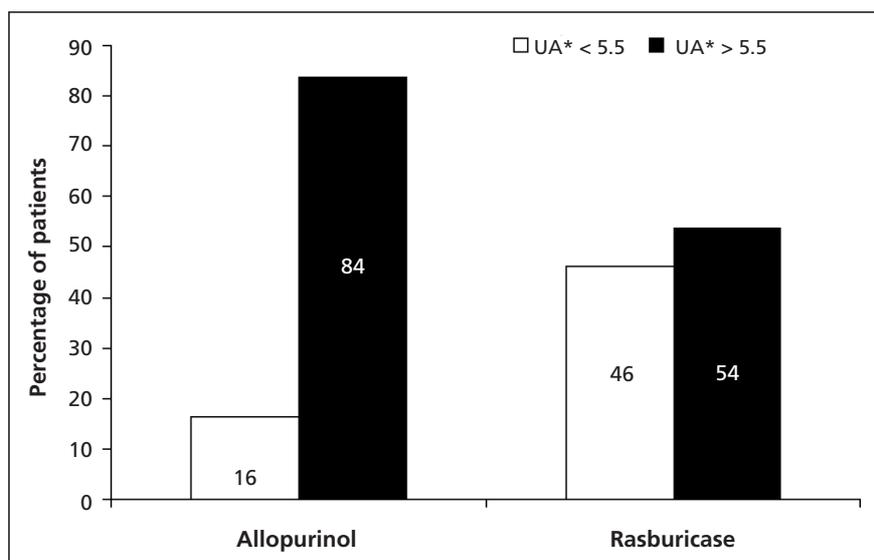


commonly used of urate-lowering agents. It blocks the conversion of ipoxanthine and xanthine to uric acid, resulting in a significant reduction of SUA levels and a urinary excretion of these molecules. The half-life of allopurinol is less than 12 hours, due to both, a rapid conversion to its metabolite, oxypurinol, and renal excretion. The half-life of oxypurinol is approximately 24 hours and its clearance correlates directly with creatinine clearance. Therefore the clinical effects of allopurinol are probably mediated by oxypurinol. In patients with healthy renal function a dose of 300-600 mg of al-

lopurinol daily appears safe and achieves therapeutic levels of oxypurinol. Nevertheless the maintenance dose of allopurinol must be reduced in patients with renal insufficiency to avoid accumulation of oxypurinol, as the following:

- for a creatinine clearance between 50-90 mL/min the dose should be 200 mg/d
- for a creatinine clearance between 10-50 mL/min the dose should be 100 mg every 2 days
- for a creatinine clearance less than 10 mL/min the dose should be 100 mg every 3 days

Figure 4. Rasburicase administration and Allopurinol. Percentage of patients with Allopurinol and Rasburicase. *UA = serum uric acid levels. (Chi-Square = 7.87, $p = 0.005$).



On the other hand, uricosuric agents (such as probenecid or sulfinpyrazone) should not be used in patients with renal insufficiency⁸.

Siu et al recently conducted a prospective, randomised, controlled trial of 54 hyperuricemic patients with chronic kidney disease using allopurinol therapy for 12 months⁹. Results of the study showed that allopurinol therapy significantly decreased SUA levels in hyperuricemic patients with mild to moderate chronic kidney disease and preserved kidney function during 12 months of therapy compared with controls. Nevertheless, the results of this study are limited by the concomitant use of angiotensin-converting enzyme inhibitors and angiotensin receptors blockers that not allow to delineate the beneficial effect contributed by these antihypertensive medications in the decrease in blood pressure and preservation of kidney function. In our experience, the average dose of allopurinol (300 mg per day) in patients with chronic kidney disease, if correctly titrated to serum creatinine levels, resulted often inadequate to decrease SUA < 7.60 mg/dL.

In conclusion, our data suggest that rasburicase administration in renal failure patients had an anti-hyperuricemic effect even if at the dosage of 0.02 mg/kg/day, very lower than dosage that's usually used for tumor lysis syndrome prevention (0.20 mg/kg), without any side effect in all patients. After 7 days, the rasburicase therapy showed more antihyperuricemic effect in men (59%) than in women (46%) suggesting the role of estrogen.

Further studies are needed to confirm these observations and to determine if rasburicase treatment of hyperuricemia in chronic renal failure patients is a useful therapeutic option.

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