



Recombinant urate oxidase (rasburicase) in the prevention and treatment of malignancy-associated hyperuricemia in pediatric and adult patients: results of a compassionate-use trial

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To confirm the efficacy of recombinant urate oxidase (rasburicase) and to establish its safety profile, we reviewed the data on 173 children and 72 adults with malignancy who were treated with this new uricolytic agent in a compassionate-use trial. Rasburicase (0.20 mg/kg) was administered intravenously daily for 1 to 7 days and could be given every 12 h for the initial 72 h. Subsequent courses were allowed at a later date. Rasburicase produced a dramatic decrease in uric acid concentrations in all patients whether they received it for prophylaxis ($n = 79$) or treatment ($n = 166$) ($P < 0.001$ in all comparisons between the levels at diagnosis and those after treatment). The median post-treatment levels were 0.5 to 0.7 mg/dl. Repeated administrations were also effective in all 11 evaluable patients. Four children and five adults had mild adverse reactions that were drug related or of unknown etiology. In two of the children, the adverse events occurred during the second course. Rasburicase is highly effective and safe in the prophylaxis or treatment of malignancy- or chemotherapy-associated hyperuricemia in children and adults. *Leukemia* (2001) 15, 1505–1509.

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Introduction

Hyperuricemia is a potentially serious complication in patients with neoplasms characterized by rapid cell proliferation and destruction.¹ It may lead to acute renal failure and delay of chemotherapy, particularly in patients with hematologic malignancies but also in those with solid tumors and a large tumor burden.² The standard treatment in the United States for the prophylaxis and treatment of hyperuricemia is allopurinol, alkalization and hydration.^{3,4} Allopurinol, an analogue of xanthine, exerts its pharmacologic effect by inhibiting the enzyme xanthine oxidase, preventing the conversion of hypoxanthine and xanthine to uric acid, and thereby reducing the renal load of uric acid. However, it may take several days for uric acid levels to normalize and the increases in xanthine levels may lead to xanthine nephropathy and urolithiasis.^{5–7}

An alternative treatment with a more rapid onset of action is the enzyme urate oxidase. Endogenous urate oxidase is present in many mammalian species, but not in humans. It catalyses the conversion of uric acid to allantoin, which is 5–10 times more soluble than uric acid and therefore readily excreted by the kidneys. Uricozyme (Sanofi-Synthelabo, France), a non-recombinant form of urate oxidase, is commercially available in France and Italy and is a highly effective uricolytic agent. However, its use is associated with hypersensitivity reactions in approximately 4.5% of patients.⁸ Recently,

a recombinant form of urate oxidase (rasburicase), isolated from *Aspergillus flavus* and expressed in *Saccharomyces cerevisiae*, has been evaluated in children with malignancy and shown to be effective and associated with a lower incidence of hypersensitivity reactions than the non-recombinant product.^{9–11} Moreover, it is also more effective than allopurinol in prophylaxis and treatment of hyperuricemia.¹¹ However, little is known about its efficacy and tolerance in adults with malignancy. In this ongoing compassionate-use program, we are evaluating the efficacy and safety of rasburicase in adults and children with cancers.

Patients and methods

Study cohorts

Between 1 January 1999 and 31 December 2000, 268 patients were entered on this ongoing compassionate-use study at 16 centers in the United States. Of these, 245 patients (173 children and 72 adults) are currently evaluable for efficacy. Twelve patients (four children and eight adults) re-entered the study and received one or more additional courses of rasburicase. Eligibility criteria included patients with cancer who have or are at high risk of hyperuricemia. There were no age limits and informed consent was obtained from all patients or their guardians. Patients were excluded if they were pregnant or lactating, had a history of significant atopic allergy, or had a documented history of asthma. In addition, patients who had a history of hypersensitivity reaction to rasburicase or Uricozyme, had received treatment with these agents within 7 days, or who had a known history of glucose-6-phosphate dehydrogenase deficiency were also excluded.

Treatment design

Rasburicase (Sanofi-Synthelabo), at a dose of 0.20 mg/kg, was diluted to a final volume of 50 ml with preservative-free sodium chloride and administered intravenously as a 30 min infusion daily for 1 to 7 days. Patients who were receiving chemotherapy, could receive the full dose (0.20 mg/kg) every 12 h for the first 72 h when the risk of developing tumor lysis is greatest. Treatment with other hypouricemic agents, eg allopurinol, was to be discontinued prior to initiation of rasburicase therapy. Patients who had received prior therapy with rasburicase or Uricozyme could be retreated on this study, if necessary, after a washout period of at least 7 days.

Laboratory determinations

Baseline laboratory evaluations included a leukocyte count, serum lactate dehydrogenase, and plasma uric acid levels.

Plasma uric acid levels were to be repeated 24 to 48 h after the last dose of rasburicase. Patients were monitored for adverse events during drug administration, and at 24 to 48 h and at 1 week after completion of rasburicase administration.

Statistical considerations

Patients who received at least one dose of rasburicase and had both pre- and post-treatment uric acid levels were included in the analysis of efficacy. All patients who had received at least one dose of rasburicase were included in the safety analysis. Efficacy in the 12 patients who received additional courses of treatment was analyzed separately. Patients were categorized as having received rasburicase for prophylaxis (baseline uric acid level at or below the upper limit of normal for age and sex) or for treatment (baseline uric acid level above the upper limit of normal for age and sex). Hyperuricemia was defined as uric acid concentration greater than 6.4, 5.9, 6.4, 7.2 or 6.4 mg/dl in patients aged 0–2, 2–12, 12–14, >14 (males), or >14 years (females), respectively.¹²

Median pre- and post-uric acid levels were compared using a paired *t*-test. Response was defined as achievement of normal uric acid levels for the 'treatment' cohort and maintenance of normal uric acid levels for the 'prophylaxis' cohort. Adverse events were graded using WHO criteria. Only those events that were considered to be related to the study drug or of unknown relationship are included.

Results

Presenting characteristics of the 173 children and 72 adults included in the efficacy analysis are shown in Table 1. The

most frequent diagnosis in the pediatric cohort was acute lymphoblastic leukemia (ALL) (71%). In adult patients, the most frequent diagnoses were acute myeloid leukemia (33%), non-Hodgkin's lymphoma (26%) and ALL (18%). Most patients had a high tumor burden as evidenced by greatly elevated lactic dehydrogenase levels and by a high leukocyte count (in patients with leukemia).

Treatment efficacy

In children presenting with hyperuricemia, there was a marked decline in uric acid levels from a median of 9.7 mg/dl (range, 6.2 to 33.6 mg/dl) at diagnosis to a median of 0.6 mg/dl (range, 0.0 to 8.1 mg/dl) post-treatment ($P < 0.001$, Table 2). All but two children achieved and maintained a normal uric acid level; they received a median of three doses of rasburicase (range, 1 to 9). The two children with an elevated uric acid level after treatment had inadequate therapy. One patient, an 8-month-old female with pre-B cell ALL, presented with a leukocyte count of $44.5 \times 10^9/l$ and a baseline uric acid of 10.8 mg/dl. The uric acid declined to 7.2 mg/dl after two doses of rasburicase. The patient was then taken off study as the investigator considered that she had completed treatment. The second patient was a 9-year-old male with small non-cleaved-cell non-Hodgkin's lymphoma. The uric acid was 11.0 mg/dl at diagnosis and declined to 8.1 mg/dl after one dose of rasburicase. The patient was taken off study as he was found to be ineligible because of a history of asthma. He was then treated with allopurinol and developed acute renal failure requiring dialysis.

All 49 adults presenting with hyperuricemia had a marked decline ($P < 0.001$) in uric acid levels from a median of

Table 1 Presenting features according to patient groups

	Pediatric <i>n</i> = 173		Adult <i>n</i> = 72	
	Treatment <i>n</i> = 117	Prophylaxis <i>n</i> = 56	Treatment <i>n</i> = 49	Prophylaxis <i>n</i> = 23
Age (years)				
Median	8	4	52	54
Range	0–18	0–17	19–85	19–90
Sex				
Male	78	37	35	10
Female	39	19	14	13
Diagnosis				
ALL	82	40	8	5
AML	14	2	19	5
CLL	0	0	4	5
CML	1	1	4	1
NHL	16	9	12	7
Hodgkin's disease	0	0	1	0
Solid tumors	4	4	0	0
Plasma cell leukemia	0	0	1	0
Lactic Dehydrogenase (U/l)				
Median	3085	1112	2701	856
Range	168–47 800	221–14 219	497–42 000	264–5031
Uric acid (mg/dl)				
Median	9.7	4.7	11.9	4.0
Range	6.2–33.6	1.2–6.9	7.0–24.3	1.1–7.2
Leukocyte count ($\times 10^9/l$) (leukemia patients)				
Median	58.7	28.8	49.1	81.3
Range	0.2–523.8	1.1–656.0	0.1–278.5	7.2–436.0

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; NHL, non-Hodgkin lymphoma.

Table 2 Efficacy of rasburicase according to patient groups

	Pediatric <i>n</i> = 173		Adult <i>n</i> = 72	
	Treatment <i>n</i> = 117	Prophylaxis <i>n</i> = 56	Treatment <i>n</i> = 49	Prophylaxis <i>n</i> = 23
Baseline uric acid (mg/dl)				
Median	9.7	4.7	11.9	4.0
Range	6.2–33.6	1.2–6.9	7.0–24.3	1.1–7.2
Post-treatment uric acid (mg/dl)				
Median	0.6	0.5	0.7	0.7
Range	0.0–8.1	0.0–3.5	0.0–5.0	0.2–3.4
Paired <i>t</i> -test for difference in uric acid	<i>P</i> < 0.001	<i>P</i> < 0.001	<i>P</i> < 0.001	<i>P</i> < 0.001
No. of responses				
No. of patients (%)	115 (98%)	56 (100%)	49 (100%)	23 (100%)
Number of doses given				
Median	3	3	3	2
Range	1–9	1–10	1–10	1–7
Number of days of dosing				
Median	3	3.5	3	3
Range	1–7	1–9	1–7	1–7

11.9 mg/dl (range, 7.0 to 24.3 mg/dl) to 0.7 mg/dl (range, 0.0 to 5.0 mg/dl); they received a median of three doses (range, 1 to 10) of rasburicase.

Prophylactic efficacy

The 56 children and 23 adults who received rasburicase as prophylaxis had a significant decline in uric acid levels (*P* < 0.001 in both groups; Table 2). All children and adults maintained a normal uric acid level after a median of three (range, 1 to 10) and two (range, 1 to 7) doses of rasburicase, respectively.

Repeated administration

Of the 12 patients who received additional courses of rasburicase, all but one achieved a normal uric acid level. The exception was a 77-year-old female in blastic phase of chronic lymphocytic leukemia. Her uric acid level increased slightly from 7.2 mg/dl to 7.4 mg/dl, but she received only one dose of rasburicase as repeated treatment.

Response in patients requiring hemodialysis

Four children and six adults required hemodialysis (Table 3). Eight of the 10 patients presented with acute renal insufficiency and nine had an elevated uric acid concentration at diagnosis. All had resolution of hyperuricemia after rasburicase treatment. The indications of hemodialysis were hyperphosphatemia (*n* = 2), azotemia (*n* = 5) or both (*n* = 3); at the time of the start of hemodialysis, all of them had very low uric acid level. All patients recovered from renal failure.

Treatment toxicities

All patients were included in the safety analysis. A total of 283 treatment courses were administered (one course was given to

256 patients, two courses to 10 patients, and three and four courses to one patient each). Overall, four children and five adults had adverse events that were considered to be drug-related or of unknown etiology. The majority of the events were mild. In the pediatric group, adverse events in first treatment courses were grade 2 vomiting (one patient) and grade 1 itching (one patient). In second courses, one child experienced grade 1 urticaria, and one developed grade 3 diffuse generalized rash and grade 1 pruritus. In adult patients, the events reported in first courses consisted of grade 1 wheezing, grade 1 skin rash, grade 3 fever and grade 2 myalgia, grade 1 headache, and grade 2 edema in one patient each.

A 15-year-old boy who presented with acute renal insufficiency, died on the second day of treatment from cardiac and respiratory failure; on the day of expiration, the uric acid concentration was 0.5 mg/dl. Another 63-year-old man with large cell lymphoma who presented with acute renal sufficiency, died of intracranial hemorrhage on day 6 of treatment; his uric acid concentration was 0.7 mg/dl after treatment. None of the two deaths were related to rasburicase treatment.

Discussion

This study confirms that rasburicase is an effective, well-tolerated uricolytic agent for children and adults. The majority of patients had hematologic malignancies and all had hyperuricemia at presentation or were considered to be at very high risk for developing this complication. All evaluable patients achieved normal uric acid levels and most maintained very low levels during treatment. As this compassionate-use study only required the measurement of uric acid levels within 24 to 48 h after the last dose of rasburicase, it is not possible to determine the rapidity of response. However, we have shown a dramatic decrease in uric acid by 4 h post-dose in children with leukemia or lymphoma treated with rasburicase,⁹ and this experience has been confirmed by other investigators in the United States and Europe.^{10,11}

Hemodialysis was not required in any of the 131 pediatric patients with leukemia or lymphoma treated in our previous

Table 3 Clinical features and outcome of 10 patients requiring hemodialysis

Patient	Presenting features				Post-treatment uric acid level (mg/dl)	Hemodialysis		
	Age (year)	Diagnosis	Creatinine level (mg/dl)	Uric acid level (mg/dl)		Need	Reason	Outcome
1	0.4	B cell ALL	0.9	14	1.8	Yes	hyperphosphatemia on day 5	recovered
2	11	AML	1.2	10.8	0.9	Yes	azotemia and fluid overload on day 2	recovered
3	14	ALL	5.3	33.6	0.7	Yes	azotemia on day 4	recovered
4	14	Burkitt lymphoma	3.0	22.3	0.5	Yes	azotemia on day 1	recovered
5	19	AML	1.5	8.9	0.5	Yes	hyperphosphatemia and azotemia on day 3	recovered
6	26	ALL	2.2	2.8	2.4	Yes	hyperphosphatemia and azotemia on day 3	recovered
7	40	Large cell lymphoma	1.9	13.1	Not done	Yes	hyperphosphatemia and azotemia on day 2	recovered
8	65	Follicular lymphoma	3.5	12.7	0.7	Yes	azotemia on day 3	recovered
9	66	Plasma cell leukemia	1.8	7.2	0.7	Yes	hyperphosphatemia on day 3	recovered
10	71	AML	BUN 87 mg/dl	18.3	3.6	Yes	azotemia on day 3	recovered

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML chronic myeloid leukemia; BUN, blood urea nitrogen.

study,⁹ nor among 107 patients (17 adults and 90 children) in the study of Lascombes *et al*¹⁰ and 27 childhood cases in the study of Goldman *et al*.¹¹ By contrast, 10 of 245 patients in this compassionate-use study required dialysis after the start of rasburicase. Patients in this study were highly selected and were at particularly high risk of tumor lysis syndrome and acute renal failure. In this regard, eight of these 10 patients presented with renal insufficiency (the total number of patients with renal insufficiency at diagnosis is unknown because the data was not collected in this compassionate-use program). The indications for hemodialysis in them were hyperphosphatemia or azotemia or both. In fact, all 10 patients had very low uric acid levels after rasburicase treatment, even at the time of starting hemodialysis. A study is planned to determine the utility of rasburicase in patients who presented with compromised renal function.

Rasburicase was well tolerated in both children and adults. Only nine patients had adverse events that were possibly related to rasburicase treatment or whose etiology is unknown. None were severe. Although three children and three adults developed possible evidence of hypersensitivity (pruritus, hives, rash, wheezing or edema), there was no severe acute hypersensitivity reaction, the major toxicity of the non-recombinant product.⁸ In our initial study, only one of 131 patients developed bronchospasm and hypoxemia.⁹ That patient presented with hypereosinophilia and pneumonia and had received chemotherapy preceding the onset of symptoms. The symptoms might have been related to the release of cytokines from eosinophils caused by chemotherapy. A low prevalence of hypersensitivity was also observed in other studies. In the study of Lascombes *et al*,¹⁰ two of the 107 patients developed grade 1 skin rashes which were possibly drug-related. No hypersensitivity was reported among 27 children treated in the study of Goldman *et al*.¹¹

Antibodies to rasburicase were not detected in any of the 27 patients in the study of Goldman *et al*,¹¹ but were found

in 17 of the 121 patients tested in our previous study⁹ and in 7% of the patients in the study of Lascombes *et al*.¹⁰ The development of antibodies to rasburicase raises the question of whether subsequent administration of the enzyme might result in an increased incidence of hypersensitivity reactions and lesser clinical efficacy. In this regard, of the 15 subsequent courses given to 12 patients in this study, only two were associated with possible hypersensitivity reactions and all but one of the repeated administrations were effective. The exception was a patient who received only one dose of rasburicase during repeated treatment, rendering it difficult to judge whether or not this represents a failure to respond to rasburicase treatment.

This study confirmed that rasburicase is a safe and highly effective agent for the treatment or prophylaxis of malignancy-associated hyperuricemia in both pediatric and adults patients. However, as with other oxidative agents, it should not be used in patients with known glucose-6-phosphate dehydrogenase deficiency. One of the by products of breakdown of uric acid to allantoin⁹ is hydrogen peroxide, which can induce hemolytic anemia or methemoglobinemia in patients with glucose-6-phosphate dehydrogenase deficiency. Whether rasburicase can be safely administered to patients with a history of clinically significant atopic allergy or bronchial asthma will require additional studies.

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Appendix

The following institutions and principal investigators also participated in the study: Children's Healthcare of Atlanta, Atlanta, GA – C Davis; Children's Hospital Medical Center of Northern California, Oakland, CA – C Hastings; Children's Hospital of Michigan, Detroit, MI – M Hamre; Children's Hospital of Oklahoma, Oklahoma City, OK – W Meyer; Children's Hospital of Orange County, Orange, CA – V Shen; Children's Hospital of Pittsburgh, Pittsburgh, PA – M Wollman; Children's Mercy Hospital, Kansas City, MO – G Woods; Children's National Medical Center, Washington, D.C. – G Reaman; Jonathan Jacques Children's Cancer Center, Long Beach, CA – J Finklestein; Pediatric-Arthritis-Hematology-Oncology-Immunology, Las Vegas, NV – R Oseas; Saint Peter's University Hospital, New Brunswick, NJ – L Ettinger; Texas Children's Cancer Center, Houston, TX – S Blaney; Texas Oncology, PA, Dallas, TX – S Goldman; University of North Carolina School of Medicine, Chapel Hill, NC – J Blatt; University of Rochester Medical Center, Rochester, NY – B Asselin; University of Texas Southwestern Medical Center at Dallas, Dallas, TX – R Bash.