Rasburicase for Tophaceous Gout Not Treatable with Allopurinol: An Exploratory Study

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ABSTRACT. ***Objective.*** To evaluate the short-term safety and outcome of 2 different experimental applications of rasburicase 0.2 mg/kg (monthly vs daily) in patients with tophaceous gout not treatable by allopurinol. Rasburicase could be useful for patients with gout that is unresponsive to allopurinol or who cannot tolerate the therapy.

Methods. Five patients received 6 monthly infusions of rasburicase (Group 1) and 5 received 5 daily infusions (Group 2).

Results. In Group 1, serum uric acid (SUA) level decreased significantly, from 612.6 ± 162.4 μmol/l at baseline to 341.2 ± 91.8 μmol/l after 6 infusions (p = 0.001). Changes in tophus area were observed in 2 patients. In Group 2, daily infusions produced a rapid, marked decrease in SUA level during treatment. Yet SUA levels measured at 1 month (511.5 ± 128.4 μmol/l) and 2 months (572 ± 96.2 μmol/l) after treatment were not significantly lower than at baseline (573.6 ± 48.2 μmol/l). No patient from Group 2 showed reduced tophus size. Eight of 10 patients experienced an adverse event, the most common being gout flare despite prophylactic treatment with colchicine.

Conclusion. Monthly infusions of rasburicase appear to be a possible therapy for severe gout not treatable by other means. Tolerance of rasburicase in gout appears to be diminished by frequent triggering of gout attacks, and hypersensitivity reactions might be an important limitation to longterm therapy. (First Release Sept 15 2007; J Rheumatol 2007;34:2093–8)

Key Indexing Terms:
GOUT RASBURICASE TREATMENT ALLOPURINOL RENAL FAILURE ALLERGY

Gout is due to monosodium urate crystal deposition in tissues and can be cured by the dissolution of pathogenic crystals, by sustained lowering of serum uric acid (SUA) concentration below the saturation point for monosodium urate[1,2]. Allopurinol is the most widely used urate-lowering drug and it is usually effective and well tolerated[3]. However, about 25% of patients who take allopurinol report side effects, and 5% discontinue the medication because of intolerance[4-6]. Moreover, allopurinol can be contraindicated because of potential adverse drug interactions with, for example, azathioprine. Therapy may also be of limited efficacy when renal impairment prevents sufficient dosage, because the risk of allopurinol-related toxic effects are increased in the presence of significant renal impairment[5,7,8]. Alternative therapy is therefore needed for patients who cannot tolerate allopurinol or for whom the drug is contraindicated or not effective enough[4,9]. Use of probenicid is an alternative, but the drug can be contraindicated because of the risk of nephrolithiasis or ineffective because of coexistent renal failure[5,9,10]. Other uricosuric drugs have similar contraindications and have become unavailable even in Europe, since the benzbromarone recall. Allopurinol desensitization has proven to be a valid strategy[11], but may be applied only for patients in whom mild skin intolerance develops and may be considered cumbersome and potentially dangerous[4,9].

Another potential option is the use of urate oxidase, which oxidates uric acid into allantoin. Allantoin is 5–10 times more soluble than uric acid and is therefore easily excreted by the kidneys[12]. The only presently available uricase is rasburicase, which has been shown to be effective in preventing and treating hyperuricemia in patients with acute tumor lysis syndrome and has been approved for this indication[12,13]. Rasburicase is a recombinant Aspergillus uricase, and its use leads to a lower incidence of hypersensitivity reactions than the previously available nonrecombinant enzyme uricozyme[13]. Although rasburicase has not been approved for the management of gout, some investigators have reported successful use for patients with severe tophaceous gout[14,15]. Data regarding optimal dosage and interval between infusions are lacking, owing to the absence of clinical studies of rasburicase in patients with gout.

The objective of this descriptive study was to evaluate the short-term safety and outcome of 2 different experimental applications of rasburicase, monthly versus daily, 0.2 mg/kg, in patients with tophaceous gout and renal failure.

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MATERIALS AND METHODS

Patients. We retrospectively reviewed the charts of 10 patients who had been treated with rasburicase in our 2 institutions. All patients had severe tophaceous gout proven by monosodium urate crystal demonstration and mild to severe renal failure. Rasburicase treatment was used because either patients could not tolerate allopurinol (n = 5) or disease was unresponsive to the dosage allowed because of renal impairment (n = 5). Each patient had given informed consent for the use of the rasburicase treatment. Allopurinol desensitization was not attempted in the 5 intolerant patients because all had experienced a severe erythematous maculopapular or morbilliform eruption occurring following initiation of allopurinol. Uricosuric drug therapy was not used because of coexistent renal failure in all patients, attributed to gout nephropathic features in 4 of them.

Rasburicase administration. Rasburicase 0.2 mg/kg (Fasturtec®; Sanofi-Synthelabo, Paris, France) was administered intravenously. The drug was reconstituted in 1-ml solvent to a concentration of 1.5 mg/ml, and the infusion was delivered over 30 min. Patients received premedication with intravenous solumedrol 60 mg and were closely monitored during and after the infusion.

As there was no validated treatment scheme for rasburicase in gout, we used 2 different experimental plans. Patients from the first institution (Group 1; 5 patients) received 6 monthly infusions of rasburicase, whereas patients from the second institution (group 2; 5 patients) received 5 daily infusions, as recommended for the management of hyperuricemia during tumor lysis syndrome[12]. Prophylaxis against acute attacks during the treatment was performed by use of colchicine (0.5–1 mg) in 8 patients. Two patients did not receive colchicine, because they could not tolerate the drug. In these patients, nonsteroidal antiinflammatory drugs (NSAID) were not used because of the presence of renal failure. No patient took allopurinol while receiving rasburicase. Patient 1 has been recently described elsewhere[16].

Clinical and biological assessment. Clinical data collected included age, sex, duration of disease, presence or absence of uratic arthropathic or uratic nephropathic features, and use of concomitant colchicine therapy. Quantitative changes in tophus size were evaluated by direct physical measurement[17]. For each patient, SUA and creatinine clearance levels were measured just before each rasburicase infusion. The number of acute flares of gout during the treatment course was recorded.

Statistical analysis. All data are presented as the mean ± SD. Change in results after rasburicase treatment was measured by Student's paired t-test. A value of $p < 0.05$ was considered significant.

RESULTS

Demographic features. The mean age of patients was 67.3 ± 12.4 years and the mean duration of disease was 21.5 ± 13.9 years. All patients (8 men) had tophaceous gout and all had renal failure (mean creatinine clearance 32.5 ± 14 ml/min). The mean SUA level for all subjects measured just before rasburicase treatment was 608.1 ± 110.7 µmol/l. All patients had uratic arthropathic features, and 4 had uratic nephropathic features. Patient age, disease duration, and SUA and creatinine clearance levels were comparable between the 2 groups (Table 1).

Efficacy of monthly rasburicase infusions. Patient 3 received only one infusion because of subsequent acute attacks of arthritis. Therefore, 4 patients underwent 6 monthly infusions. SUA level declined progressively during the 6 months (Figure 1), from a mean of 612.6 ± 162.4 µmol/l at baseline to 341.7 ± 91.8 µmol/l at the end of treatment ($p = 0.001$). Creatinine clearance level before and after treatment did not change significantly: 32.2 ± 7.5 ml/min and 33.8 ± 8.5, respectively. Figure 2 shows a time course of urate concentration within 1 month following one infusion for one patient (Patient 5, first infusion). Urate oxidase induced a deep decrease in urate concentration with a maximal decline at Day 7. This effect was transient, because SUA level slowly rebounded but did not reach pretreatment level after 30 days. At 6 months, change in tophus area was observed in 2 of the 4 patients. All the numerous small intradermal tophi disappeared from the hands of Patient 1, and the size of a voluminous tophus in the pad of the right thumb of Patient 2 was greatly decreased (Figure 3).

Efficacy of daily rasburicase infusions. For Group 2 patients, the mean plasma uric acid concentration prior to treatment was 573.6 ± 48.2 µmol/l. Figure 4 shows the change in SUA level over 2 months, after 5 daily rasburicase infusions. In all patients, rasburicase produced a rapid, marked decrease in urate concentration that remained below the limit of detection during the entire treatment course in 4 patients. Nevertheless, following the 5 days of treatment, uric acid concentration progressively rose again to the pretreatment SUA level in all patients. The urate level measured at 1 month and 2 months after the end of treatment was 511.5 ± 128.4 µmol/l and 572 ± 96.2 µmol/l, respectively, but was not significantly lower than that at baseline. No patient from Group 2 showed reduced tophus size, and renal function was not modified by the daily rasburicase infusions.

Tolerance of rasburicase. Ten patients received a total of 50 infusions. Eight of the 10 experienced an adverse event that was possibly treatment related, the most common being gout flare, despite prophylactic treatment with colchicine (0.5–1 mg daily) in 8 patients. The number of patients with gouty arthritis flare was higher in Group 2 (4/5 patients) than in Group 1 (2/5 patients). Oral colchicine was the first-line agent for treating acute flares. In some patients, NSAID were also administered for a very brief period, during which creatinine level was carefully monitored. One patient from Group 1 required subsequent intravenous corticosteroids because colchicine and NSAID were not effective enough. Two patients from Group 1 experienced an allergic reaction, bronchospasm, or cutaneous eruption, at the sixth infusion, which led to discontinuation of the rasburicase therapy in both. Both adverse events resolved quickly. Hemolysis after rasburicase administration was not observed in any patient (Table 2).

DISCUSSION

We investigated the use of rasburicase in patients with tophaceous gout and renal impairment whose disease was resistant to allopurinol or who could not tolerate the therapy. Renal failure is an important limitation to managing gout with conventional urate-lowering therapy, because uricosuric agents may have diminished efficacy and allopurinol dosage must be adjusted to the rate of creatinine clearance[8,18]. By contrast, rasburicase, which is degraded via peptide hydrolysis, appears as an interesting option in patients with renal impairment because its clearance is independent of renal function[19].

Rasburicase has been developed to prevent and treat chemotherapy-induced hyperuricemia in adults and chil-

Table 1. Characteristics of patients with severe tophaceous gout before rasburicase treatment. Patients 1 to 5 (Group 1) received 6 monthly rasburicase infusions. Patients 6 to 10 (Group 2) received 6 daily rasburicase infusions.

Patient	Sex	Age, yrs	Duration of Gout, yrs	SUA, µmol/l	Creatinine Clearance, ml/min	Uratic Nephropathy	Uratic Arthropathy	Colchicine, mg/day
1	F	56	4	446	35	Yes	Yes	1.0
2	M	84	46	563	44	No	Yes	1.0
3	M	71	8	609	30	No	Yes	no
4	M	80	10	564	26	No	Yes	0.5
5	M	79	16	882	26	Yes	Yes	1.0
6	M	57	23	576	55	No	Yes	1.0
7	F	68	43	570	19	No	Yes	1.0
8	M	74	20	648	20	Yes	Yes	0.5
9	M	57	19	630	17	Yes	Yes	no
10	M	47	26	594	54	No	Yes	1.0

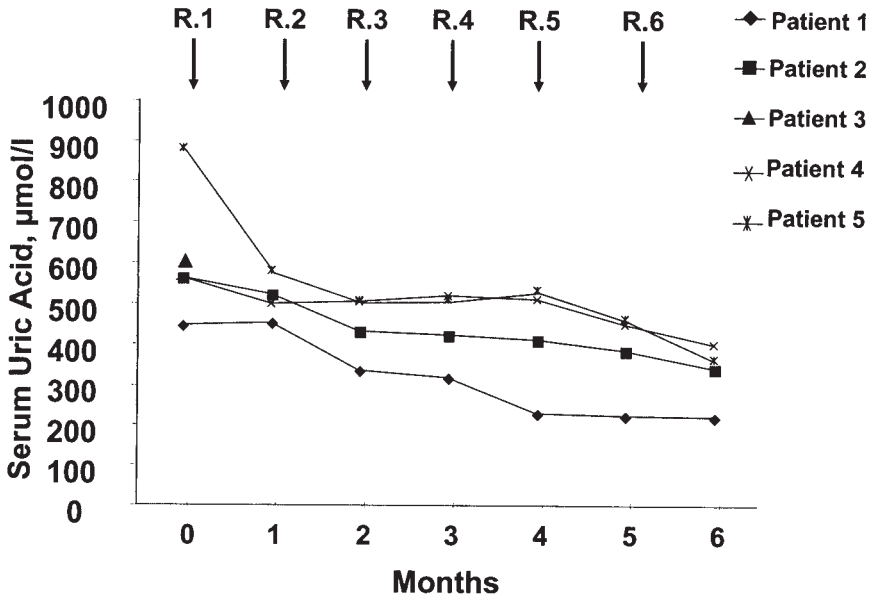

Figure 1. Time course of SUA level over 6 months with monthly rasburicase infusions (arrows, R.1–R.6). Uric acid levels were determined before the infusion.

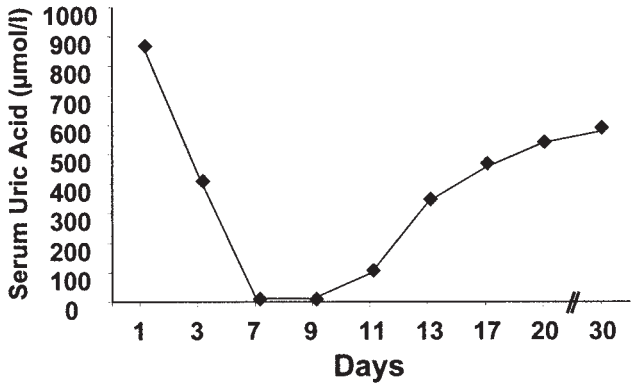

Figure 2. SUA level within a month after the first rasburicase infusion in Patient 5.

dren[20]. In this indication, Fasturtec® is administered daily intravenously at 0.2 mg/kg per dose for 5 days[21,22]. We thus compared this dosage and administration with a monthly regimen that we had planned in our patients considering the transient effect of this drug and the need for a sustained decrease of uricemia to treat gout[21].

In accord with results obtained for tumor lysis syndrome[13,20], one rasburicase infusion induced a rapid and marked decrease in urate concentration in patients with tophaceous gout and renal impairment. It should be kept in mind that rasburicase can degrade uric acid in blood samples at room temperature, which leads to further minimizing measured SUA levels[12,22]. This observation could partly explain the transient and sharp decrease in SUA levels that were below

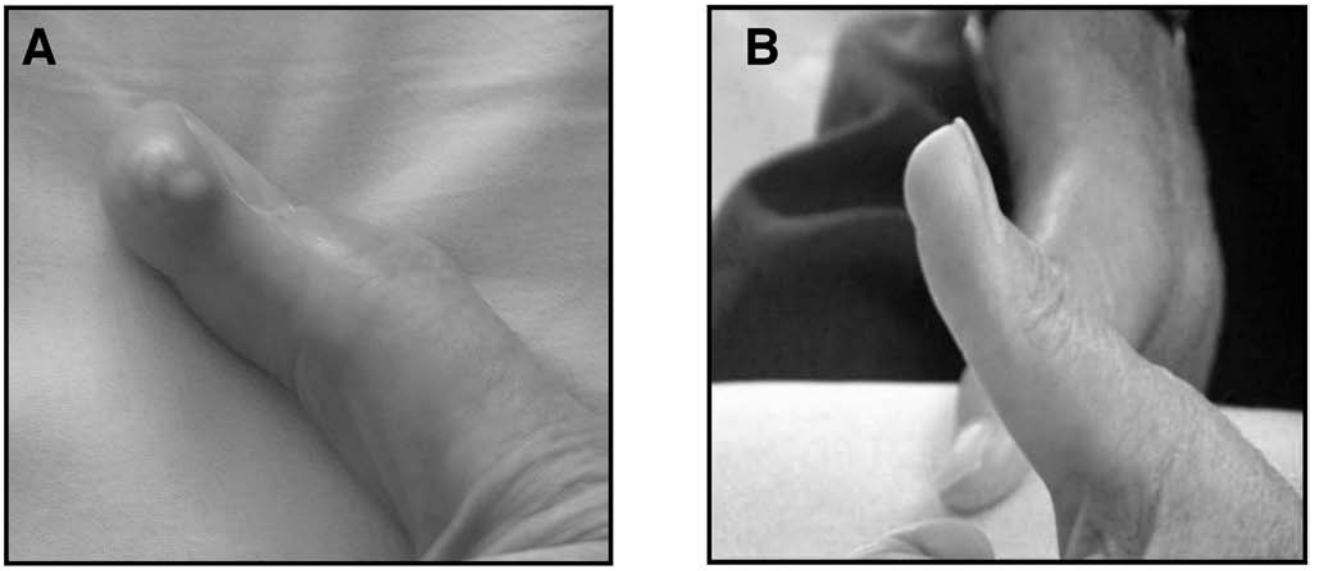

Figure 3. Effect of a 6-month rasburicase treatment on tophus size of Patient 2. A. Tophaceous bulk in the thumb before infusions. B. Significant decrease of the tophus size after 6 infusions.

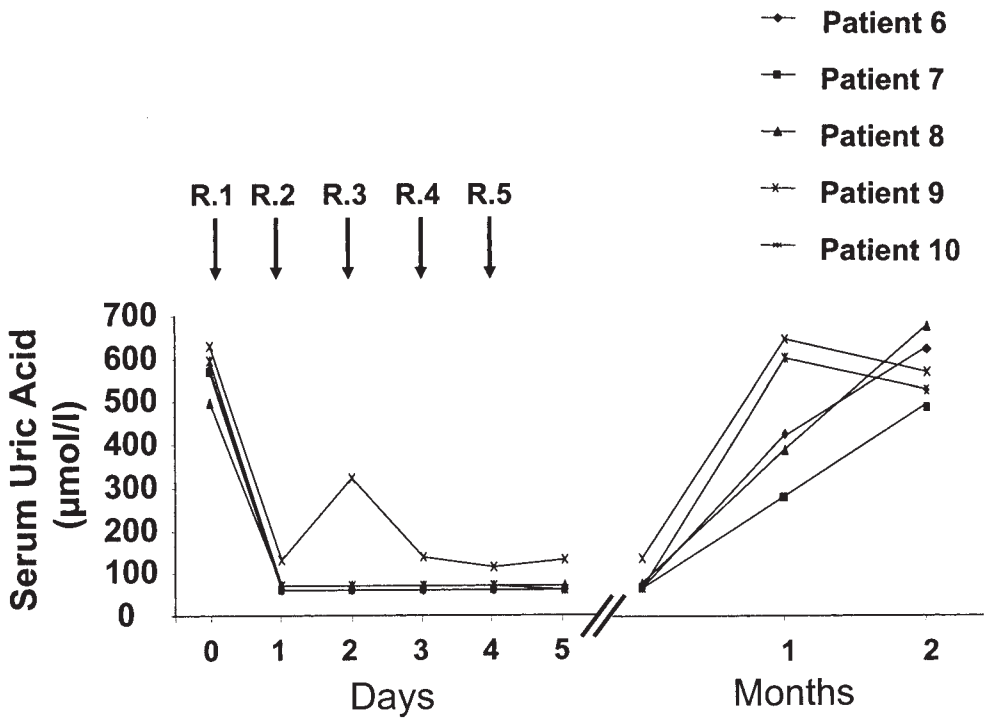

Figure 4. Time course of SUA level with 5 daily rasburicase infusions.

the limit of detection in 4 patients following the daily infusion course. Nevertheless, the efficacy of rasburicase was transient, and 5 daily infusions did not allow a sustained lowering of SUA concentration. This finding likely reflects the pharmacokinetics of rasburicase. Pharmacokinetic studies in patients treated with the drug at 0.2 mg/kg showed that the steady-state level of rasburicase is reached by Day 2 and that the mean plasma terminal half-life is 21 ± 12 hours[12].

Drugs that lower SUA concentrations and thus deplete urate stores are the definitive longterm disease-modifying treatment for gout[10]. The aim of urate-lowering therapy is to permanently reduce the urate concentration below 360 µmol/l (6.0 mg/dl)[5]. Our results indicate that this goal cannot be reached by a limited number of daily infusions of rasburicase. By contrast, 5 monthly infusions of Fasturtec® were effective in lowering urate level below or around the target urate level,

Table 2. Tolerance of rasburicase. Patients 2 and 4 experienced bronchospasm and urticarial reaction, respectively, following the sixth infusion of rasburicase.

Patient	No.Acute Flares	Allergy
1	8	No
2	0	Yes
3	2	No
4	0	Yes
5	0	No
6	2	No
7	3	No
8	2	No
9	0	No
10	1	No

360 µmol/l, in our patients. Nevertheless, the time course of the SUA level within a month for one patient suggests that measurement of SUA concentration every month is not a relevant outcome to evaluate the efficacy of rasburicase. Indeed, the SUA level within a month increased steadily to the level before the infusion, after a maximal decline at 1 week. Most importantly, the substantial regression of hand tophi in 2 patients indicates that urate deposition can be rapidly mobilized by short-term monthly infusions of rasburicase, which can be started even late in the course of the disease.

Reports of 2 cases described the successful use of longterm intermittent rasburicase infusions (0.15 to 0.2 mg/kg) for severe tophaceous gout resistant to conventional urate-lowering agents[14,15]. In both cases, Fasturtec® decreased the size of tophi and lowered SUA level after at least 6 months' treatment. These reports also highlighted the tendency for arthritic flares following each infusion.

Gout attacks were the main adverse event encountered with rasburicase treatment in our series, despite concomitant therapy with colchicine and corticosteroids. The severity of these attacks led to discontinuation of the treatment in one patient. The acute flares occurred generally early, following the first infusions of rasburicase, and their frequency tended to decrease over time. Their occurrence was explained by the rapid reduction in SUA level that followed rasburicase infusions, which led to the liberation of crystals from the synovium or cartilage into the joint space. One of the byproducts of uric acid breakdown by uricase is hydrogen peroxide. Therefore, G6PD deficiency contraindicates treatment with rasburicase because of the risk of hemolysis[23]. None of our patients showed this potentially severe complication. Rasburicase is known to be antigenic, and this raises the concern that repeated administration of the drug would decrease its efficacy and increase the risk of hypersensitivity. Studies have demonstrated that time to detection of antibodies ranges from 1 to 6 weeks after administration[21], and that presence of antibodies is not associated with adverse events[22]. We did not observe a decrease in efficacy over time in our patients who received the drug intermittently during 6 months. Nevertheless, the incidence of hypersensitivity reactions was higher in this group than in the daily administration group. All reactions were mild and resolved readily with discontinuation of rasburicase.

Although this exploratory study is, to our knowledge, the largest reported series of patients with tophaceous gout treated with rasburicase, it deals with only a limited number of patients with gout exposed to the drug, and our results must be interpreted with caution. However, we confirm that rasburicase has a powerful ability to reduce SUA concentration in patients with gout. Repeated intermittent administration appears to be a possible therapy for severe gout not treatable with other therapy. Tolerance of rasburicase in gout appears to be marred by the very frequent triggering of gout attacks. Moreover, hypersensitivity reactions can occur, as in 2 of our patients, and are likely to be an important limitation to longterm therapy with this drug. New medications can be expected to expand treatment options in allopurinol-intolerant patients. The orally administered nonpurine inhibitor febuxostat has demonstrated efficacy and safety in phase II and III trials[24,25]. Its efficacy and good tolerance were reported in a short series of allopurinol-intolerant patients[10]. Finally, a novel uricase, coupled to polyethylene glycol, is currently under investigation. The incorporation of polyethylene glycol is expected to reduce antigenicity and prolong half-life of the enzyme[26]. These newer therapies will be a good alternative to the use of rasburicase in these difficult to treat patients, if they prove to be safer.

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