Urate oxidase (rasburicase) for treatment of severe tophaceous gout

Bruno Vogt

Division of Nephrology and Hypertension, University Hospital Inselspital, Berne, Switzerland

Keywords: cyclosporine; gout; gout tophi; hyperuricaemia; kidney transplant; rasburicase; urate oxidase

Introduction

Gout is a clinical disorder caused by deposition of urate crystals in a joint leading to acute inflammatory response with acute pain. In severe and longstanding gout, the crystals accumulate in soft tissues such as cartilage, subcutaneous tissue or even veins leading to the development of tophi responsible for very large deposit formations and disability. Most cases of gout present with the sudden onset of severe acute arthritis in a peripheral joint in the leg.

Urate oxidase, or uricase (EC 1.7.3.3), is a peroxisomal liver enzyme that catalyses the enzymatic oxidation of uric acid into the more water-soluble allantoin (Figure 1). Urate oxidase is an endogenous enzyme found in most mammals but not in humans. During primate evolution, the inactivation of the hominoid urate oxidase gene was caused by independent nonsense or frameshift mutations and has taken a two-step deterioration process, first in the promotor and second in the coding region [1]. Two nonsense mutations were found in the human urate oxidase gene, which confirms, at the molecular level, that the urate oxidase gene in humans is non-functional [2–3]. Because uric acid is a powerful scavenger of free radicals, it has been proposed that uric acid plays an important role in protection hominoids from oxidative damage and the prolonged live span [1,4].

Urate oxidase is used in humans for the control of increased serum uric acid in patients with acute tumour lysis syndrome after receiving chemotherapy. Rasburicase (SR 29142), a recombinant urate oxidase expressed in Saccharomyces cerevisiae, has been demonstrated to be superior to allopurinol in the control of uric acid in a randomized trial of paediatric and adult patients at risk of acute tumour lysis syndrome [5,6]. However, only few case reports address the potential role of urate oxidase for treatment of severe tophaceous gout. A French group treated three heart transplant patients with uncontrollable gout with non-recombinant urate oxidase and observed shrinking of tophi and improved mobility of the fingers in all three patients [7]. Phillips and co-workers used rasburicase for treatment of severe tophaceous gout refractory to high-dose allopurinol in a patient with end-stage renal disease and observed a regression of gout tophi [8]. The treatment was well tolerated in all reported patients and produced no adverse effects.

We analysed efficacy and safety of rasburicase in the long-term control of hyperuricaemia in an adult kidney transplant patient with severe tophaceous gout.

Case report

A 33-year-old female patient suffered from severe tophaceous gout. Kidney transplantation was performed 8 years ago for end-stage renal disease caused by bilateral vesico-ureteral reflux disease in childhood. Renal function remained stable (creatinine clearance 30 ml/min). Hyperuricaemia was present since the time of end stage renal failure with eight to 12 gout attacks per year treated with steroids and colchicine. Allopurinol was not given because of allopurinol allergy. Anorectic behaviour and therapy with cyclosporine together with loop diuretics contributed to hyperuricaemia. During the last 6 years, severe tophaceous gout developed with large deposits in all fingers of both hands as well as in the feet. The tophi recurred despite repetitive surgical removal and led to significant disability due to previous sensory loss (Figure 2).

A therapy with the recombinant urate oxidase rasburicase (Fasturtec, i.e. SR29142 from Sanofi-Synthelabo, Geneva, Switzerland) 0.15 mg/kg body weight i.v. every second week was started. Serum uric acid decreased from baseline levels of ~850 μM to values below 50 μM during the first week after therapy and increased steadily during the subsequent weeks to levels before therapy during the first 6 month
treatment period. Thereafter, and for the rest of the 3
years of monthly rasburicase therapy, serum uric acid
decreased from 850 to 658 μM (mean of three values).
Following rasburicase injection, serum uric acid
decreased despite a concomitant decrease in urinary
excretion of uric acid (fractional excretion of uric acid
decreased from 8% to 3%), indicating metabolism of
uric acid unrelated to renal elimination. In the presence
of decreased fractional excretion of uric acid, one
potential mechanism for the decrease in serum uric acid
is the elimination of uric acid metabolites by transport
mechanisms similar to that of uric acid. Proteinuria of
0.20–0.35 g/24 h remained stable during the 3 years of
therapy. Rasburicase therapy was well tolerated and
produced no adverse effects besides occasional episodes
of inflammation observed during the first 2 months
of therapy. These episodes of mild inflammation of
multiple joints (symmetrically fingers, knees and feet)
disappeared when the dose was lowered and the
interval between two doses was prolonged. With
0.15 mg/kg body weight of rasburicase every fourth
week, the patient remained without side effects during
3 years of follow-up. No gout attack occurred since
the start of rasburicase therapy. The size of the tophi
decreased substantially and the patient’s functional
capacity improved dramatically (Figure 3).

Discussion

Urate oxidase is an enzyme that catalyses the conver-
sion of uric acid into allantoin, which is 10 times more
soluble than uric acid and more readily eliminated by
the kidney. Humans and certain primates lack this
enzyme. Administered intravenously, urate oxidase is a
potent and fast-acting urate-lowering drug used for the
prevention of acute urate nephropathy during tumour
lysis following cytolysis. As demonstrated in
this patient, to the best of our knowledge the first renal
transplant patient, urate oxidase can be used to reduce
serum uric acid to a degree that will facilitate the
resorption of tophi and improve functional capacity in
patients with severe gout who have allopurinol intol-
erance to.

Rasburicase, a recombinant urate oxidase, which is
an urolytic agent, and has been developed for the
prevention and treatment of chemotherapy-induced
hyperuricemia and acute renal failure induced by
tumour lysis [6, 9]. In this indication, the recommended
dosage is 0.20 mg/kg per day for 5–7 days. Significant
reductions from baseline in plasma uric acid levels were
seen in a randomized comparative trial of rasburicase
versus allopurinol in pediatric patients at high risk of
tumour lysis syndrome. The efficacy and safety of
rasburicase for the prevention and treatment of hyper-
uricaemia during induction chemotherapy of aggressive
non-Hodgkin’s lymphoma has been demonstrated in
several clinical studies such as the recent GRAAL1
(Groupe d’Etude des Lymphomes de l’Adulte Trial on
Rasburicase Activity in Adult Lymphoma) study [5].
Rasburicase was well tolerated in clinical trials, with
skin rashes reported in <2% of patients [6]. Therefore,
short-term administration of rasburicase can be
regarded as well tolerated with very few side effects.
However, to date no experience of long-term therapy
with rasburicase exists. In this regard, our patient represents the first report on a 3 year rasburicase therapy. The very few side effects observed at the beginning of therapy disappeared after 2 months of treatment, and then the patient was event free for the remaining 3 years. Two reasons may account for this: first, the immunosuppressive therapy with cyclosporine A and prednisone administered concomitantly might facilitate the excellent tolerance, and second, rasburicase has a high degree of purity since the structure of the molecule is maintained by a specific purification process [10].

The dramatic regression of gout tophi in the finger tips indicates that a substantial amount of uric acid tissue deposits can be mobilized by long-term rasburicase therapy.

Treatment of severe gout remains a challenge in medicine. Today, therapeutic options to decrease serum uric acid consist of diet and uricosstatic agents like allopurinol [11]. Drugs known to increase serum uric acid like diuretics and cyclosporine A usually cannot be avoided as in the present case. Benz bromarone, an uricosuric drug, is not in use any more because its association with fulminant liver failure. Therefore, urate oxidase agents might open new therapeutic possibilities in patients with severe uncontrolled gout. Furthermore, allopurinol allergy, albeit rare, represents another interesting indication for these patients [12].

Despite the excellent tolerance for 3 years of the patient described above, allergic reactions remain a possible threat that need to be addressed in further studies with the urate oxidase rasburicase.

**Acknowledgements.** The author thanks Dr Stefan Kohler, Geneva, Switzerland, for suggestions and critical reading of the manuscript. This work was supported by a grant from the Swiss National Foundation for Scientific Research (No. 32-57205.99) and a research grant from Sanofi-Synthelabo, Geneva, Switzerland. Part of this work was presented in abstract form at the Annual Meeting of the Swiss Society of Nephrology 2002; St Gallen, Switzerland.

**Conflict of interest statement.** None declared.

**References**


Received for publication: 16.8.04
Accepted in revised form: 12.11.04