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Case Report

Urate oxidase (rasburicase) for treatment of severe tophaceous gout

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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). Hyperuricemia 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 hyperuricemia. 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 base line 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

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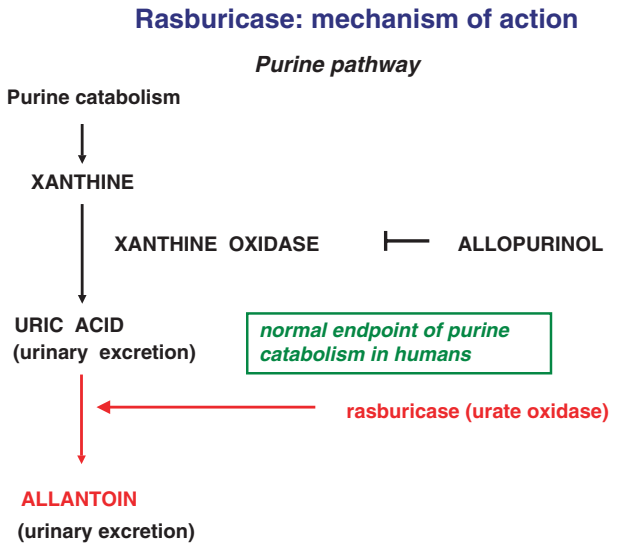

Fig. 1. Purin pathway. Allopurinol blocks the conversion of xanthine to uric acid. The urate oxidase rasburicase catalyses the oxidation of uric acid to allantoin, a highly water-soluble metabolite readily excreted by the kidney.

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 decrased 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 conversion 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

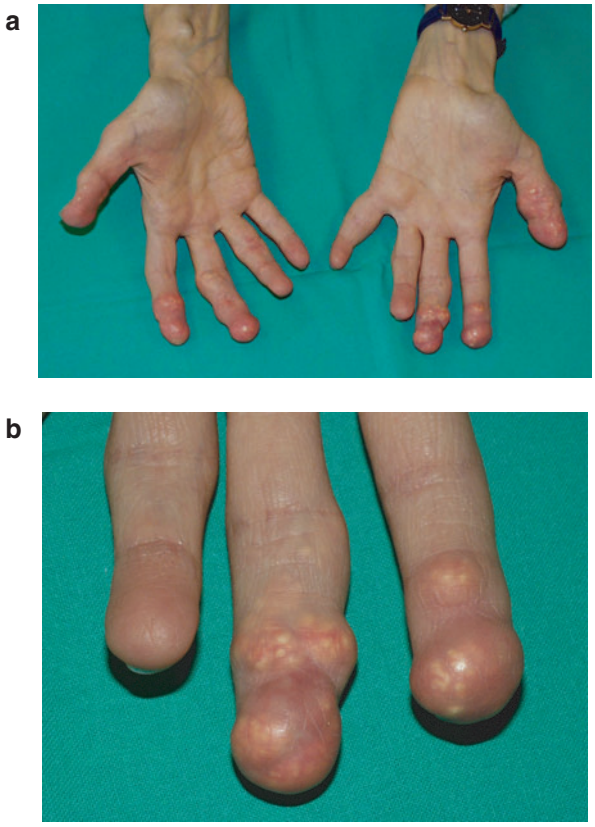

Fig. 2. Left and right hand from the 33-years-old female patient with severe gout tophi on both hands leading to pain and functional disability.

lysis following cytolytic therapy. 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 intolerance 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 hyperuricaemia 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

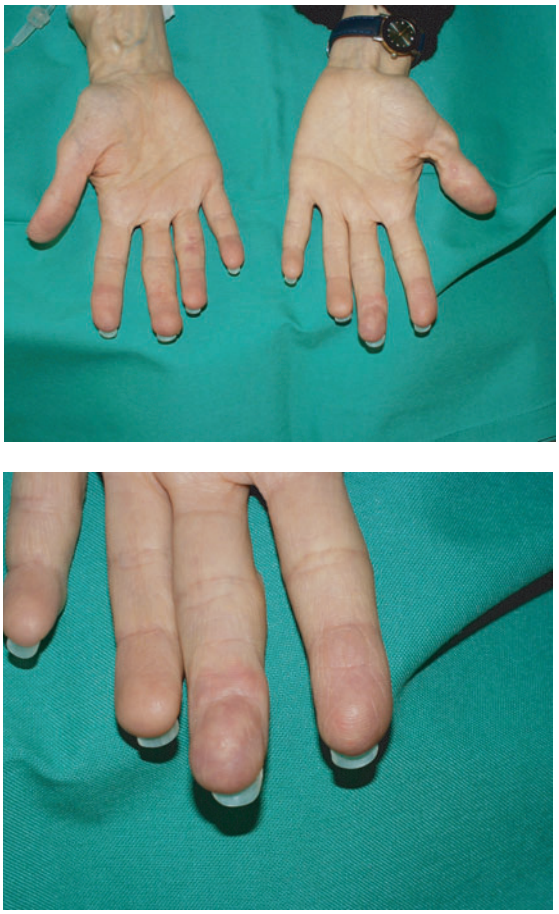

Fig. 3. Left and right hand from the 33-year-old female patient after 12 months of therapy with the urate oxidase rasburicase.

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 uricostatic 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. Benzbromarone, 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.

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Conflict of interest statement. None declared.

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