ADIS DRUG EVALUATION

Drugs 2006; 66 (4): 529-545
0012-6667/06/0004-0529/$44.95/0

Rasburicase

A Review of its Use in the Management of Anticancer Therapy-Induced Hyperuricaemia

Vicki Oldfield and *Caroline M Perry*

Adis International Limited, Auckland, New Zealand

Various sections of the manuscript reviewed by:

B. Culleton, Department of Nephrology, University of Calgary, Calgary, Alberta, Canada; ***S. Howard***, Pediatric Hematology-Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee, USA; ***A. Bosly***, Faculté de Médecine, Cliniques Universitaires Saint-Luc, Brussels, Belgium; ***S. Goldman***, Department of Hematology-Oncology, North Texas Hospital for Children at Medical City Dallas, Dallas, Texas, USA; ***C.-S. Ueng***, Department of Pharmacy Services, Baylor University Medical Center, Dallas, Texas, USA; ***M. Schreiber***, Department of Nephrology and Hypertension, The Cleveland Clinic Foundation, Cleveland, Ohio, USA.

Data Selection

Sources: Medical literature published in any language since 1980 on 'rasburicase', identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE search terms were 'rasburicase' and ('hyperuricaemia' or 'hyperuricemia'). EMBASE search terms were 'rasburicase' and ('hyperuricaemia' or 'hyperuricemia'). AdisBase search terms were 'rasburicase' and ('hyperuricaemia' or 'hyperuricemia'). Searches were last updated 14 February 2006.

Selection: Studies in patients with chemotherapy-induced hyperuricaemia who received rasburicase. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Rasburicase, hyperuricaemia, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability, tumour lysis syndrome.

Contents

Summary

Abstract

Intravenous rasburicase (Elitek®, Fasturtec®) is the first recombinant uricolytic agent. It is indicated for the management of anticancer therapy-induced hyperuricaemia in paediatric patients in the EU and US, and in adult patients in the EU.

Rasburicase is effective and generally well tolerated in adult and paediatric patients with, or at risk of developing, anticancer therapy-induced hyperuricaemia. It is associated with potentially serious haematological adverse events and hypersensitivity reactions, which must be considered prior to and during administration; rasburicase is contraindicated in patients predisposed to haemolysis or methaemoglobinaemia and in patients with glucose-6-phosphate dehydrogenase deficiency. Unlike allopurinol, rasburicase acts on existing uric acid concentrations. Rasburicase treatment resulted in significantly less systemic exposure to uric acid and a quicker therapeutic response than allopurinol in paediatric patients; further studies are needed to determine the comparative efficacy and tolerability of rasburicase versus allopurinol in adult patients. Although further pharmacoeconomic data would be useful, rasburicase was most cost effective for the prevention of hyperuricaemia in children and for treatment of this condition in adults. Thus, rasburicase is a useful option for the prophylaxis or treatment of anticancer therapy-induced hyperuricaemia in both adult and paediatric patients.

Pharmacological Properties

Rasburicase, a recombinant form of urate oxidase, facilitates the renal clearance of uric acid via conversion to allantoin, a readily excretable compound with 5- to 10-fold greater solubility at urinary pH than uric acid. Intravenous rasburicase has potent, dose-dependent uricolytic activity in healthy volunteers at doses of 0.05–0.2 mg/kg. The conversion of uric acid to allantoin by rasburicase results in accumulation of allantoin and the formation of hydrogen peroxide, a by-product of uric acid oxidation. Rasburicase is immunogenic; anti-rasburicase antibodies were detected in 11% of patients with haematological malignancies 28 days after administration of rasburicase in clinical trials.

Steady-state conditions are reached after 2–3 days of once-daily administration of intravenous rasburicase 0.15 or 0.2 mg/kg. There is no evidence of accumulation of rasburicase in plasma after multiple-dose administration.

Although the precise metabolic pathway of rasburicase has not been determined, it is suspected of undergoing peptide hydrolysis like other proteins. There is minimal renal clearance and the pharmacokinetic properties of rasburicase are not expected to vary in patients with renal dysfunction.

Therapeutic Efficacy

Hyperuricaemia was rapidly prevented or corrected in ≥99% of adult and paediatric leukaemia and lymphoma patients with or at risk of hyperuricaemia who received intravenous rasburicase 0.15 or 0.2 mg/kg once daily for 5–7 days in two multicentre dose-finding trials. A significant decrease in plasma uric concentration was evident at 4 hours after rasburicase administration, regardless of baseline uricaemia status.

In a randomised, nonblind, multicentre trial, intravenous rasburicase 0.2 mg/kg once daily for 5–7 days was significantly more effective than oral allopurinol 10 mg/kg per day for the prevention or treatment of anticancer therapy-induced hyperuricaemia in paediatric leukaemia or lymphoma patients aged 0–17 years with or at risk of hyperuricaemia; the reduction in exposure to uric acid over 96 hours after drug administration was significantly greater with rasburicase than allopurinol. Rasburicase recipients had a significantly greater reduction in plasma

uric acid concentration than allopurinol recipients at 4 hours after administration of the study drug.

In two noncomparative, nonblind, multicentre studies, rasburicase 0.2 mg/kg once daily for 1–7 or 3–7 days prevented or corrected anticancer therapy-induced hyperuricaemia in adult and paediatric leukaemia, lymphoma or multiple myeloma patients with, or at risk of, hyperuricaemia. All adult patients (aged 25–85 years) who received rasburicase treatment for ≥3 days achieved a response to treatment, defined as normalisation of plasma uric acid concentration after 3 days of chemotherapy and throughout the duration of chemotherapy.

Tolerability

A single course of treatment with rasburicase was generally well tolerated in adult and paediatric patients in clinical trials, with the most frequently observed adverse events (vomiting, fever, nausea and headache) being those expected in patients with advanced malignancies receiving concomitant anticancer therapy. Most adverse events were mild and transient, lasting <1–2 days. Rasburicase and allopurinol were similarly tolerated in paediatric recipients.

Rasburicase is associated with infrequent but serious haematological adverse effects, including haemolytic reactions, which occurred in <1% of 703 patients, according to a pooled analysis of data from clinical trials and an expanded access programme. Other serious rasburicase-related adverse events occurred in ≤5% of rasburicase recipients in clinical and compassionate-use trials and in the expanded access programme; these included fever, neutropenia with fever, respiratory distress, sepsis, neutropenia, mucositis and allergic reactions including anaphylaxis and rash. Acute renal failure, which occurred in ≤1% of 703 patients, was considered to be unrelated to rasburicase aside from one case of tubular nephritis. No deaths that occurred in the clinical trials or compassionate-use studies were considered by investigators to be related to rasburicase.

1. Introduction

Hyperuricaemia, which is variously defined as a plasma or serum uric acid concentration >7.0 mg/dL[1] (≈420 μmol/L) or >8.0 mg/dL[2] (476 μmol/L), arises from reduced excretion and/or increased formation of uric acid. Although it occurs most frequently in patients with gout, hyperuricaemia is also associated with various hereditary disorders and malignancies.[3] It is a hallmark of laboratory tumour lysis syndrome, which is characterised by a range of metabolic abnormalities that may arise spontaneously but often occur after the initiation of cytolytic anticancer therapy.[1,2] Metabolic abnormalities usually occur within 5 days of the initiation of anticancer therapy and result from the release of purines and other intracellular products following tumour cell lysis.[1]

Laboratory tumour lysis syndrome is defined as the presence of at least two of the metabolic abnormalities listed in table I. Although metabolic abnormalities are usually reversible with prophylactic or early treatment, they may have serious clinical consequences including acute renal failure and death; clinical tumour lysis syndrome is defined as the presence of laboratory tumour lysis syndrome and at least one of the most significant clinical complications, which include renal insufficiency, seizures, cardiac arrhythmias or sudden death.[2] The incidence of laboratory tumour lysis syndrome, which has been reported in 42% of adults and 70% of children with haematological malignancies, is much higher than the incidence of clinical tumour lysis syndrome, which occurred in 6% of adults and 3% of children.[4]

Hyperuricaemia is the most common metabolic abnormality observed in tumour lysis syndrome patients who eventually develop acute renal failure.[5] Uric acid is the end product of purine catabolism in humans (figure 1), and production of uric acid is increased following the post-cytolysis release of purines in response to anticancer therapy.[6] Uric

Table I. Metabolic abnormalities occurring in tumour lysis syndrome (TLS)[1,2,7]

Metabolic abnormality	Criteria for diagnosis of laboratory TLS[a]	Pathophysiology	Clinical symptoms
Hyperuricaemia	≥476 μmol/L (≈8.0 mg/dL) or 25% increase from BL	Catabolism of purine nucleic acids released after cytolysis	Acute renal failure, haematuria, oliguria/anuria, seizure, anorexia, oedema, hypertension, metabolic acidosis, nausea, vomiting, diarrhoea, pruritis, lethargy, malaise
Hypocalcaemia	≤ 1.75 mmol/L or 25% decrease from BL	Precipitation of calcium phosphate complex due to increased phosphate concentration	Ventricular arrhythmia, bradycardia, cardiac failure, ECG changes, hypotension, heart block, tetany, muscle cramps or spasms, paraesthesia, syncope, seizure, anxiety, hallucinations, confusion, delirium, impaired memory, irritability, renal failure due to acute nephrocalcinosis, sudden death
Hyperkalaemia	≥6.0 mmol/L or 25% increase from BL	Post-cytolysis release of intracellular K^+	Ventricular arrhythmia, asystole, bradycardia, cardiac arrest, ECG changes, muscle weakness or cramps, lethargy, anorexia, diarrhoea, paraesthesia, ascending flaccid paralysis, nausea, vomiting, syncope, sudden death
Hyperphosphataemia	≥2.1 mmol/L (children) or ≥1.45 mmol/L (adults) or 25% increase from BL	Post-cytolysis release of intracellular $PO4^-$	Intrarenal calcification, metastatic calcification, nephrolithiosis, acute obstructive uropathy, oliguria/anuria, azotaemia, muscle cramps, tetany, arrhythmias, seizure, nausea, vomiting, diarrhoea, lethargy

a From the Cairo-Bishop definition of laboratory TLS.[2]

BL = baseline; **K^+** = potassium; **$PO4^-$** = phosphate

acid is poorly soluble in urine and overwhelms the excretory capacity of the renal tubule, leading to hyperuricaemia.[5] In the presence of an acidic pH, uric acid crystals may precipitate in the renal tubules and distal collecting system and obstruct urine flow, causing uric acid nephropathy and acute renal failure.[5,7] Hyperuricaemia may be present prior to anticancer therapy and patients with pretreatment hyperuricaemia are at a greater risk of developing clinical tumour lysis syndrome.[2]

Rasburicase (Elitek®, Fasturtec®)[1] is an intravenously administered uricolytic agent indicated for the management of acute hyperuricaemia in patients with haematological or solid tumour malignancies. This article reviews the use of rasburicase in adult and paediatric patients who have, or are at risk of developing, anticancer therapy-induced hyperuricaemia.

2. Pharmacodynamic Properties

Data on the pharmacodynamic properties of rasburicase are from one study in 28 healthy volunteers (available as an abstract).[10] Additional information is from the manufacturer's prescribing information[11,12] and the scientific discussion produced by the European Medicines Agency (EMEA).[13]

Rasburicase, a recombinant form of urate oxidase, facilitates the renal clearance of uric acid via 5-hydroxyisourate-mediated oxidation to allantoin (figure 1).[14] Allantoin is a readily excretable compound with 5–10 times greater solubility at urinary pH than uric acid.[14] The conversion of uric acid to allantoin by rasburicase represents a step in the purine catabolic pathway that does not usually occur in humans as, unlike other mammals, they lack endogenous urate oxidase.[9]

Intravenous rasburicase had marked dose-dependent uricolytic activity in healthy volunteers at doses of 0.05–0.2 mg/kg and reduced plasma uric acid concentrations were maintained over 6 days with once-daily administration.[10] Increasingly large, but not dose-proportional, decreases from baseline in plasma uric acid concentration were observed at 8 hours after administration of single intravenous doses of rasburicase 0.05 mg/kg (−78%), 0.1 mg/kg (−84%), 0.15 mg/kg (−92%) and 0.2 mg/kg (−96%) in 16 healthy volunteers.[10] At day 6, study partici-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

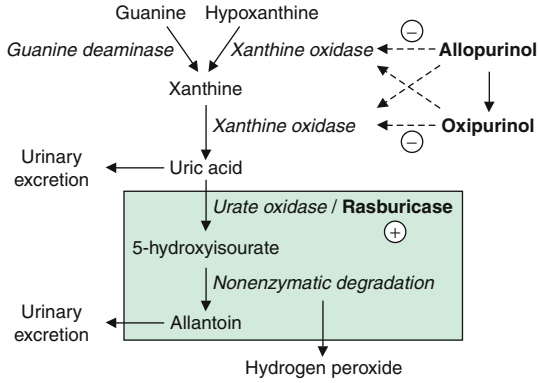

Fig. 1. Schematic representation of the effects of rasburicase, allopurinol and oxipurinol (the active metabolite of allopurinol)[8] on purine catabolism. The grey area depicts the enzymatic conversion of uric acid to allantoin, a process that does not occur naturally in humans as, unlike other mammals, they lack endogenous urate oxidase.[9] – indicates inhibition of xanthine oxidase by allopurinol and oxipurinol; + indiacates metabolism of uric acid by rasburicase.

pants who had received rasburicase 0.1, 0.15 or 0.2 mg/kg once daily for 5 days had plasma uric acid concentrations 95%, 97% and 95%, respectively, below baseline concentrations.[10]

The rasburicase-mediated conversion of uric acid to allantoin by rasburicase results in accumulation of allantoin and the formation of hydrogen peroxide, which is a by-product of uric acid oxidation.[13] Allantoin is water-soluble and is excreted renally[13] whereas hydrogen peroxide undergoes catalase-mediated conversion to oxygen and water.[14] Patients with glucose-6-phosphate dehydrogenase deficiency or inherited anaemia may be at risk of haemolysis as a result of elevated hydrogen peroxide levels, and rasburicase is contraindicated in these patients (section 7).[13]

Rasburicase is immunogenic; anti-rasburicase antibodies were detected in 64% (18 of 28) of healthy volunteers 1–6 weeks after intravenous rasburicase administration for up to 5 days (dosage not specified).[11] Rasburicase antibodies were detected in 11% (24 of 218) of patients with haematological malignancies 28 days after administration of rasburicase in clinical trials; however, antibodies may develop after this time and the true incidence of antibody development may be higher.[11]

There was no evidence of a metabolic interaction between rasburicase and allopurinol, cytarabine, methylprednisolone, methotrexate, mercaptopurine, tioguanine (thioguanine), etoposide, daunorubicin, cyclophosphamide or vincristine *in vitro*.[11] However, no drug interaction studies have been conducted with rasburicase in humans.[12]

3. Pharmacokinetic Properties

The pharmacokinetic properties of intravenous rasburicase were investigated in adult and paediatric leukaemia or lymphoma patients with or at risk of hyperuricaemia in two dose-finding studies discussed in section 4.1.[15,16] Pharmacokinetic results from one dose-finding trial[16] are reported as an abstract.[17] Additional information is from the EMEA scientific discussion.[13]

3.1 Absorption and Distribution

Steady-state conditions are reached after 2–3 days of once-daily administration of intravenous rasburicase 0.15 or 0.2 mg/kg.[13] There is no evidence of accumulation of rasburicase in plasma after multiple-dose administration; rasburicase maximum plasma concentration (C_{max}) and area under the

Table II. Overview of the pharmacokinetic properties of rasburicase (RAS) in adult and paediatric patients with or at risk of anticancer therapy-induced hyperuricaemia. Patients in two dose-finding studies received intravenous RAS 0.15 or 0.2 mg/kg once daily as a 30-minute infusion (n = 10,[17] 30[15]). Mean values are reported

Parameter	RAS dose (mg/kg)					
	day 1			day 5		
	0.15[17]	0.15[15]	0.2[15]	0.15[17]	0.15[15]	0.2[15]
C_{max} (μg/L)	2.79	3.13[a]	3.88[a]	3.50	3.36[a]	4.50[a]
AUC_{24} (μg • h/L)	28.0	32.9	45.2	36.5	34.4	47.3
$t_{½}$ (h)				17.4	16.0	21.1

a At the end of infusion.

AUC_{24} = area under the plasma concentration-time curve from 0 to 24 hours; **C_{max}** = maximum plasma concentration; **$t_{½}$** = plasma elimination half-life.

plasma concentration-time curve (AUC) values were similar after single- and multiple-dose administration (table II).[15,17]

The distribution of rasburicase is thought to be limited to the vascular space.[13] The volume of distribution for rasburicase after intravenous infusion of 0.2 mg/kg in leukaemia and lymphoma patients is 110–127 mL/kg, which is similar to the physiological vascular volume.[13] Rasburicase, a protein, is not suspected of binding to plasma proteins.[13]

3.2 Metabolism and Elimination

Although the precise metabolic pathway of rasburicase has not been determined, it is suspected, like other proteins, of undergoing peptide hydrolysis; the metabolism of rasburicase is not likely to be altered in patients with impaired hepatic function.[13] Rasburicase has a long plasma elimination half-life, which ranged from 16 to 21 hours after administration of rasburicase 0.15 or 0.2 mg/kg in leukaemia or lymphoma patients (table II).[15,17] Rasburicase is not expected to interact with other drugs metabolised by the cytochrome P450 (CYP) 1A, 2A, 2B, 2C, 2E and 3A isoenzymes.[11]

There is minimal renal clearance of rasburicase and the pharmacokinetic properties of rasburicase are not expected to vary in patients with renal dysfunction.[13] Although the clearance of rasburicase is ≈35% higher in children and adolescents than in adults, resulting in decreased exposure to rasburicase in younger patients (actual values not reported), no dosage adjustments are required in paediatric recipients.[13] Exposure to allantoin, the product of rasburicase-mediated conversion of uric acid, may be increased in renally impaired patients.[13]

4. Therapeutic Efficacy

4.1 Dose-Finding Trials

Two multicentre dose-finding studies evaluated the therapeutic efficacy of once-daily intravenous rasburicase in adult and/or paediatric leukaemia and lymphoma patients with or at risk of hyperuricaemia (table III).[15,16] Patients were paediatric and adolescent (aged ≤20 years; n = 131)[15] or paediatric and adult (aged 1–80 years; n = 107).[16] The trial in paediatric and adult patients is available as an abstract only and design details are limited.[16]

Patients in both trials received rasburicase once daily as a 30-minute intravenous infusion for 5–7 days.[15,16] The target dosage was that which reduced the plasma uric acid concentration to below the hyperuricaemic threshold (table IV).[15,16] In the trial in paediatric and adolescent patients,[15] the target dosage was defined as the dose that corrected hyperuricaemia within 48 ± 2 hours after treatment was initiated and prevented hyperuricaemia for up to 24 hours after treatment in 14 consecutive patients.[15] Postadministration plasma uric acid concentrations were measured at 4 and 12 hours and then every 12 hours thereafter.[15]

Table III. Diagnoses required for inclusion of adult and/or paediatric patients (pts) in clinical trials evaluating the therapeutic efficacy of once-daily intravenous rasburicase 0.15 or 0.2 mg/kg for the prevention or treatment of anticancer therapy-induced hyperuricaemia

Study	Diagnoses
Dose-finding trials	
Pui et al.[15]	B-cell ALL; ALL with an initial leukocyte count ≥50 × 10^9/L or a lymphomatous presentation and a large tumour burden; stage III or IV B-cell or lymphoblastic NHL with a large tumour burden; any leukaemia or NHL with plasma uric acid ≥8 mg/dL and either serum creatinine or LDH >2 × ULN
Lascombes et al.[16] a	ALL, ANL or NHL
Fixed-dose trials	
Goldman et al.[18]	ALL with peripheral leukocyte count ≥25 × 10^6/L; stage III or IV NHL; any childhood leukaemia or lymphoma with plasma uric acid ≥8 mg/dL
Coiffier et al.[19]	NHL (diffuse large B-cell, peripheral T-cell, Burkitt's and anaplastic large-cell lymphomas and indolent lymphomas transformed into a more aggressive subtype)
Wang et al.[20]	ALL; high-grade lymphoma; AML; multiple myeloma

a Abstract.

ALL = acute lymphocytic leukaemia; **AML** = acute myelogenous leukaemia; **ANL** = acute non-lymphoid leukaemia; **LDH** = lactate dehydrogenase; **NHL** = non-Hodgkin's lymphoma; **ULN** = upper limit of normal.

Table IV. Effect of intravenous rasburicase (RAS) on plasma uric acid concentration in adult or paediatric patients (pts) with or at risk of anticancer therapy-induced hyperuricaemia. Data are from two multicentre, dose-finding trials,[15,16] a randomised, nonblind, multicentre trial,[18] two noncomparative trials[19,20] and three compassionate-use studies.[21-23] Pts with leukaemia, lymphoma, multiple myeloma or other haematological malignancies or solid tumours received RAS as a 30-minute infusion before or during anticancer therapy.[a] Where specified, results were reported for the intention-to-treat population[18] and mean[18,19] or median[15,20-23] values are depicted

Study	Age of pts (y)	Dosage regimen (mg/kg) [duration; d][b]	Baseline characteristics: plasma uric acid concentration (mg/dL)	Baseline characteristics: uricaemia status[c] (no. of pts)	Results: post-treatment plasma uric acid concentration (mg/dL)	Results: response rate (% of pts without hyperuricaemia at study end)
Dose-finding trials						
Lascombes et al.[16]	1–80	RAS 0.15	NR	HU and NU[d] (107)	NR	99
Pui et al.[15]	0.08–20	RAS 0.15 or 0.2[e]	9.7	HU (65)	1**	100
			4.3	NU (66)	0.5**	100
Fixed-dose trials						
Goldman et al.[18]	0.3–17	RAS 0.2	7.7	HU and NU[d] (27)	≈1[f,g]	NR[h]
		ALP 10	6.8	HU and NU[d] (25)	≈2.3[f,g]	NR[h]
Coiffier et al.[19]	25–85	RAS 0.2	≈5.3[g]	HU and NU[d] (100)	0.3[f,g]	100
Wang et al.[20]	7[i]	RAS 0.2[j]	10.5[k]	NR (18)	0.5[f,k]	100[l]
	59[i]		10.8[k]	NR (27)	0.5[f,k]	100[l]
Compassionate-use trials						
Bosly et al.[22]	0.1–17	RAS 0.2[i,m]	11.3	HU (29)	0.2*	NR
			4.2	NU (93)	0.5*	NR
	18–80		13.1	HU (27)	0.3*	NR
			4.9	NU (70)	0.3*	NR
Jeha et al.[21]	0–17	RAS 0.2[i,n]	9.2	HU (398)	0.5*	99
			4.1	NU (260)	0.5*	100
	18–90		10.8	HU (212)	0.7*	100
			4.8	NU (126)	0.7*	100
Shin et al.[23]	0–18	RAS 0.2[j]	9.1	HU (37)	NR	97[o]

a Plasma uric acid concentrations were measured at 4,[15] ≤24,[23] 48,[16] 72[19,20] or 96h[18] after administration of the first dose or 24–48h after administration of the last dose[21,22] for pts who received ≥1 dose of study drug.

b RAS was administered once daily for 1–7,[20-22] 3–5,[23] 3–7[19] or 5–7 days.[15,16,18]

c Hyperuricaemic threshold (mg/dL) defined as 6.5 in pts aged ≤13 y or 7.5 in pts >13y,[16] 6.5 in pts aged <13y or 7.5 in pts aged ≥13y,[15] >8,[18] >7.56,[19] >7.5[21,22] (>6.5 for children <13y[21]) or >ULN for age and sex.[20]

d Results were reported for combined hyper- and normouricaemic populations; 11% were hyperuricaemic.

e Eleven pts received RAS 0.15 mg/kg and the dosage was increased to RAS 0.2 mg/kg in the remaining pts.

f Statistical analysis not reported.

g Estimated from a graph.

h The primary endpoint in this trial was the uric acid AUC_{96}; results are reported in figure 2.

i Median (range not reported).

j Pts considered to be at high risk for development of hyperuricaemia received RAS 0.2 mg/kg twice daily for the first 3 days.

k Serum uric acid concentration.

l Although the hyperuricaemic threshold was not specified in this study, 100% of pts had plasma uric acid ≤1.7 mg/dL at 72h after RAS administration, which is below the generally accepted hyperuricaemic thresholds of 7[1] or 8 mg/dL.[2]

Continued next page

Table IV. Contd

m Median no. of doses was six in hyperuricaemic pts and five in normouricaemic pts.

n Median no. of doses was three.

o Pts with plasma uric acid ≤7 mg/dL.

ALP = allopurinol; **AUC_{96}** = area under the plasma concentration-time curve from the time of administration to 96 hours; **HU** = hyperuricaemic; **NR** = not reported; **NU** = normouricaemic; **ULN** = upper limit of normal; * $p < 0.001$, ** $p \leq 0.0001$ vs baseline.

Rasburicase 0.15 or 0.2 mg/kg for 5–7 days rapidly prevented or corrected hyperuricaemia in ≥99% of adult and paediatric leukaemia and lymphoma patients (table IV).[15,16] A significant decrease from baseline in plasma uric concentration was evident at 4 hours after rasburicase administration, regardless of baseline uricaemia status (table IV).[15] Plasma uric acid concentrations were reduced by ≥25% at 4 hours after the first dose of rasburicase 0.15 mg/kg in 101 patients with available data, and 0.15 mg/kg was concluded to be the effective dosage in this study.[16] In the trial in paediatric and adult patients, the median plasma uric acid concentration decreased significantly from baseline in the first 11 patients who received rasburicase 0.15 mg/kg (from 5.2 to 0.9 mg/dL; $p < 0.0001$).[15] However, a transient increase in plasma uric acid concentration was observed at 48 hours after administration in the twelfth patient to receive rasburicase 0.15 mg/kg and the dosage was increased to 0.2 mg/kg for the remaining patients; rasburicase 0.2 mg/kg was concluded to be the effective dosage in this study.[15]

Serum creatinine and phosphorous levels were reduced after rasburicase administration in the trial in paediatric and adolescent patients.[15] After 1 day of treatment, the median serum creatinine level decreased significantly from baseline in both hyperuricaemic patients (from ≈0.7 to ≈0.6 mg/dL; $p = 0.003$) and normouricaemic patients (from ≈0.5 to ≈0.4 mg/dL; $p = 0.02$) [values estimated from graphs]. Median serum phosphorous levels decreased from ≈5 to ≈4 mg/dL after 4 days of treatment in hyperuricaemic patients ($p = 0.003$; values estimated from graph); both hyper- and normouricaemic patients had serum phosphorous concentrations within the normal range by 48 hours after rasburicase treatment initiation.[15]

4.2 Fixed-Dose Trials

4.2.1 Versus Allopurinol In Paediatric Patients

A randomised, nonblind, multicentre trial compared the therapeutic efficacy of a single course of intravenous rasburicase 0.2 mg/kg once daily as a 30-minute infusion versus oral allopurinol 10 mg/kg (300 mg/m^2) per day (median 100mg three times daily) in paediatric patients aged 0–17 years.[18] Patients (n = 52) had leukaemia or lymphoma and either had, or were at risk of, hyperuricaemia (table III), and received treatment for 5–7 days. Additional inclusion criteria were life expectancy of ≥4 weeks, an Eastern Cooperative Oncology Group (ECOG) score ≤3 and Karnofsky scale score ≥30%. Postadministration plasma uric acid concentrations were measured at hours 4 and 12, and then every 12 hours until 96 hours.[18]

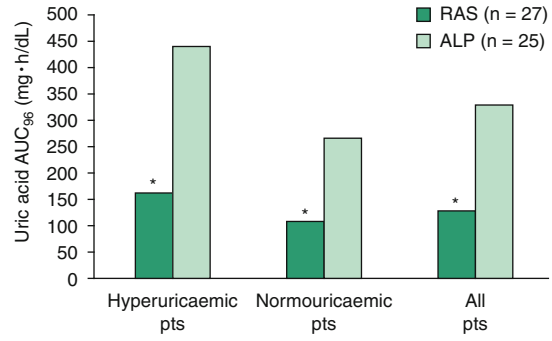

Fig. 2. Effect of treatment with intravenous rasburicase (RAS) or oral allopurinol (ALP) on systemic exposure to uric acid in paediatric patients (pts) receiving anticancer therapy. In a randomised, nonblind, multicentre trial, pts aged 0.3–17 years with leukaemia or lymphoma who either had or were at risk of hyperuricaemia (plasma uric acid >8 mg/dL) received once-daily treatment with RAS 0.2 mg/kg as a 30-minute infusion or ALP 10 mg/kg (administered in three divided doses) for 5–7 days.[18] RAS and ALP treatment was initiated prior to the start of chemotherapy. Systemic uric acid exposure was assessed using the mean uric acid area under the plasma concentration-time curve over 96 hours (AUC_{96}) [primary endpoint]. Mean results are reported for the intention-to-treat population. * $p \leq 0.0007$ vs ALP.

The primary endpoint was the area under the plasma uric acid concentration curve from the time of administration to 96 hours after administration (AUC_{96}) and results were reported for the intention-to-treat (ITT) population with the last observation carried forward for missing data.[18] There were no significant between-group differences in baseline characteristics or demographics; baseline plasma uric acid concentrations were similar in each treatment group (table IV). The mean time between study drug administration and initiation of chemotherapy was 21 hours.[18]

Rasburicase was significantly more effective than allopurinol for the prevention or treatment of anticancer therapy-induced hyperuricaemia in paediatric leukaemia or lymphoma patients.[18] The uric acid AUC_{96} was significantly lower with rasburicase than allopurinol (128 vs 329 mg • h/dL; figure 2).[18] The comparatively greater efficacy of rasburicase was independent of baseline uricaemia status; a significantly lower uric acid AUC_{96} was achieved with rasburicase by both normo- and hyperuricaemic patients (figure 2).[18]

Rasburicase also produced a faster therapeutic response than allopurinol.[18] Rasburicase recipients had a significantly greater reduction in plasma uric acid concentration than allopurinol recipients at 4 hours after administration of the study drug (figure 3).[18] All of the ten rasburicase recipients who were hyperuricaemic at baseline, and none of the five hyperuricaemic allopurinol recipients, achieved a plasma uric acid concentration <8mg/dL by, or within, 4 hours of study drug administration.[18]

4.2.2 Noncomparative Trials in Adult and Paediatric Patients

The therapeutic efficacy of intravenous rasburicase 0.2 mg/kg once daily was investigated in two noncomparative, multicentre trials in adult[19,20] and paediatric patients[20] with, or at risk of, hyperuricaemia. The trial in adults (n = 100) included patients aged 25–85 years with aggressive non-Hodgkin's lymphoma (table III) who had at least one International Prognostic Index adverse prognostic factor (lactate dehydrogenase >1 × normal level, stage III or IV disease, ECOG score ≥2, age >60 years, >1 extranodal site involved), life expectancy ≥3 months and at least one characteristic indicating a high risk of hyperuricaemia (tumour diameter

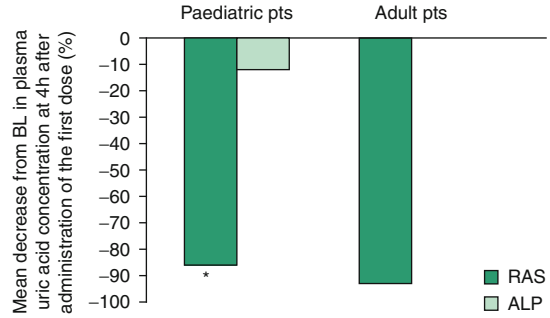

Fig. 3. Effect of intravenous rasburicase (RAS) and oral allopurinol (ALP) on plasma uric acid concentrations at 4 hours after administration of the first dose in patients (pts) with or at risk of anticancer therapy-induced hyperuricaemia. Data are from a randomised, nonblind, multicentre trial in paediatric pts (aged 0.3–17 yrs; n = 52)[18] and a noncomparative trial in adult pts (aged 25–85 yrs; n = 100).[19] Pts had leukaemia or lymphoma and received RAS 0.2 mg/kg once daily as a 30-minute infusion for 3–7[19] or 5–7[18] days. ALP 10 mg/kg was administered once daily in three divided doses.[18] Results from the trial in adult pts were estimated from a graph. **BL** = baseline; * $p < 0.0001$ vs ALP.

≥5cm, lactate dehydrogenase and/or uric acid above the upper limit of normal, increased creatinine, abnormal electrolytes or low urine volume).[19] Patients in the other study (n = 45) were aged 3–98 years, had a plasma uric acid concentration >8 mg/dL, a minimum life expectancy of at least 3 months and were scheduled to receive chemotherapy for leukaemia, lymphoma or multiple myeloma (table III).[20]

Rasburicase was administered once daily as a 30-minute infusion for 1–7[20] or 3–7 days;[19] treatment was started before or on the same day as induction chemotherapy.[19,20] Primary efficacy endpoints were not specified.[19,20] Plasma[19] or serum[20] uric acid concentrations were measured at 4[19] and 72[20] hours after the first dose and, in the adult study, at least once per day during treatment.[19]

Rasburicase prevented or corrected anticancer therapy-induced hyperuricaemia in adult and paediatric patients with, or at risk of, hyperuricaemia (table IV).[19,20] In the trial in adults,[19] all of the 95 patients who received rasburicase for ≥3 days achieved a response to treatment, defined as normalisation of plasma uric acid concentration after 3 days of chemotherapy and throughout the duration of chemotherapy. These patients experienced a ≈93% reduction from baseline in plasma uric acid concentration at 4 hours after administration (figure 3;

statistical analysis not reported)[19] [plasma uric acid concentration at 4 hours after rasburicase administration was not reported in the other study].[20]

4.3 Compassionate-Use Trials

Additional evidence of the efficacy of intravenous rasburicase in the prevention or treatment of anticancer therapy-induced hyperuricaemia in paediatric and adult patients is from three nonblind, multicentre, compassionate-use trials.[21-23] Patients with, or at risk of developing, hyperuricaemia, received rasburicase 0.2 mg/kg once daily for up to 7 days (table IV).[21-23]

Once-daily intravenous rasburicase 0.2 mg/kg prevented or corrected anticancer therapy-induced hyperuricaemia in paediatric and adult patients in these trials.[21-23] A response to rasburicase treatment, defined as a reduction in plasma uric acid to below the hyperuricaemic threshold in patients with baseline hyperuricaemia or maintenance of subthreshold plasma uric acid levels in normouricaemic patients within 24[23] or 48 hours[21,22] of the last dose, was achieved by ≥97% of paediatric and 100% of adult rasburicase recipients (table IV).[21-23] The achievement of a response to rasburicase treatment was independent of baseline uric acid levels (table IV).[21-23]

5. Tolerability

Data in this section are from the clinical trials and compassionate-use studies discussed in section 4 and from two pooled analyses included in the manufacturer's literature.[11-13] One pooled analysis (n = 347) included data on adverse events occurring in 265 paediatric and 82 adult patients who received up to 7 days of treatment with once-daily intravenous rasburicase 0.15 or 0.2 mg/kg in four trials, including the comparative and dose-finding trials discussed in section 4 and a phase II trial that evaluated the safety of rasburicase.[11-13,18] The other pooled analysis (n = 703) included data on serious adverse events occurring in the 347 patients in the first pooled analysis and in 365 adult and paediatric patients in an expanded access programme.[11]

A single course of treatment with rasburicase was generally well tolerated in adult and paediatric patients in clinical trials, with the most frequently observed adverse events (figure 4) being those expected in patients with advanced malignancies receiving concomitant anticancer therapy.[11] Most adverse events were mild and transient, lasting ≤2 days.[13]

Rasburicase is associated with infrequent but serious haematological adverse effects, including haemolytic anaemia and methaemoglobinaemia, which occurred in <1% of 703 patients in the large pooled analysis.[11] Haematological adverse events may arise from the accumulation of hydrogen peroxide, a by-product of allantoin production, and rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency, preexisting methaemoglobinaemia or other metabolic disorders known to cause haemolytic anaemia (section 7).[11,12]

Other serious rasburicase-related adverse events, including hypersensitivity reactions and respiratory events, occurred in ≤5% of rasburicase recipients in clinical and compassionate-use trials and the expanded access programme.[11,21] In the larger pooled analysis (n = 703),[11] serious rasburicase-related adverse events included fever (5%), neutropenia with fever (4%), respiratory distress (3%), sepsis (3%), neutropenia (2%), mucositis (2%) and allergic reactions including anaphylaxis and rash (both <1%).[11] Acute renal failure, which occurred in ≤1% of 703 patients,[11] was considered to be unrelated to rasburicase aside from one case of tubular

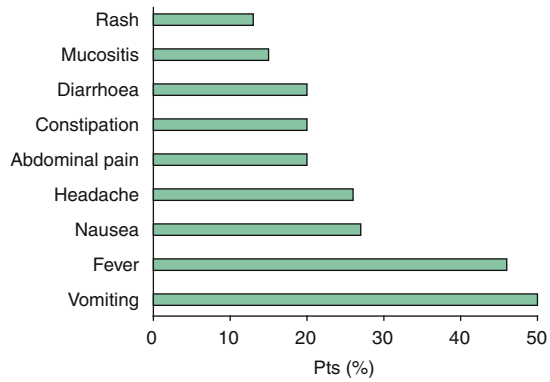

Fig. 4. Tolerability profile of intravenous rasburicase (RAS) in adult and paediatric patients (pts) with or at risk of hyperuricaemia. Data are from a pooled analysis (n = 347) of four clinical trials in which pts received RAS 0.15 or 0.2 mg/kg as a 30-minute intravenous infusion once daily for up to 7 days.[11,13] Adverse events that occurred in ≥10% of pts are depicted.

nephritis.[13] In the compassionate-use study, 25 WHO grade 3 or 4 adverse events, of which 10 were considered by investigators to be related to rasburicase, were reported in 13 of 1069 patients (1.2%); these included grade 3 haemolytic anaemia, tumour lysis syndrome, fever, albuminurea, allergic reaction and dyspnoea and grade 4 methaemoglobinaemia, hypoxia, anaphylactic shock, rigor, convulsion due to hypertensive encephalopathy and electrolyte abnormalities.[21] Grade 3 increases in liver enzymes occurred in 3 of 100 adult patients in the noncomparative trial; increases occurred within 24–48 hours of rasburicase treatment initiation and resolved without sequelae within a few days.[19] No deaths that occurred in the clinical trials or compassionate-use studies were considered by investigators to be related to rasburicase.[18,21-23]

Discontinuation of rasburicase treatment because of adverse events occurred in a small proportion of patients in clinical trials and the compassionate-use studies;[18,21] 0.9% (10 of 1069) of patients in the large compassionate-use study discontinued rasburicase treatment because of hypersensitivity reactions.[21]

Rasburicase and allopurinol were similarly tolerated by paediatric recipients in a clinical trial.[11,13,18] Almost all (96%) rasburicase recipients and 100% of allopurinol recipients reported adverse events during treatment;[13] vomiting, fever, nausea, diarrhoea and headache occurred in more rasburicase than allopurinol recipients (actual incidence not reported).[11] Adverse events considered by investigators to be related to the study drug occurred in 11% (3 of 27) of rasburicase recipients (two cases of headache and one of fever) and 4% (1 of 25) of allopurinol recipients (vomiting).[13] One rasburicase recipient discontinued treatment because of haemolysis; this patient did not have glucose-6-phosphate dehydrogenase deficiency. No allopurinol recipients discontinued treatment because of adverse events.[18]

6. Pharmacoeconomic Considerations

A decision-analysis model evaluated the cost effectiveness of intravenous rasburicase based on a retrospective review of data from the charts of paediatric and adult patients with acute lymphocytic leukaemia, acute myeloid leukaemia or non-Hodgkin's lymphoma in the UK, the Netherlands, Spain and Belgium (n = 766).[24] The incidence of hyperuricaemia and tumour lysis syndrome was estimated from the number of rasburicase treatment episodes. The costs of hyperuricaemia and tumour lysis syndrome were calculated from the healthcare payer perspective-based resource use, and the cost of rasburicase treatment was based on the average treatment duration (3–4 days) and bodyweight of patients in the compassionate-use programmes. The 5- and 10-year life expectancy of patients was based on pooled analyses of clinical trial data and UK national statistics. The incremental cost-effectiveness ratios (ICERs) for prevention and treatment of hyperuricaemia and tumour lysis syndrome with rasburicase were calculated per life-year saved considering the costs, probability of development of hyperuricaemia and tumour lysis syndrome, and the percentage of these conditions prevented by rasburicase. Rates of 100% and 90% were assumed for prevention of tumour lysis syndrome and hyperuricaemia with rasburicase.[24]

Rasburicase was generally cost effective for prevention of tumour lysis syndrome and hyperuricaemia in children, regardless of the malignancy; the ICERs were low in paediatric patients (table V).[24] The ICERs for treatment of tumour lysis syndrome and hyperuricaemia could not be calculated in children because of insufficient data.[24]

In adults, the cost effectiveness of rasburicase for prevention of tumour lysis syndrome and hyperuricaemia was dependent on the malignancy, whereas the cost effectiveness of treatment of these conditions appeared to be independent of the malignancy.[24] Prevention with rasburicase was most cost effective in adults with acute lymphocytic leukaemia or non-Hodgkin's lymphoma; the ICERs of tumour lysis syndrome and hyperuricaemia were lowest in these patients (table V). The high ICERs for rasburicase-mediated prevention of these conditions in adults with acute myeloid leukaemia reflect the short life expectancy in this population.[24] Treatment with rasburicase was cost saving in the UK regardless of the malignancy, as indicated by the negative ICERs (table V).

The ICERs of rasburicase for prevention or treatment of hyperuricaemia or tumour lysis syndrome were influenced by variables such as the life expec-

Table V. Cost effectiveness of intravenous rasburicase for the treatment and prevention of hyperuricaemia and tumour lysis syndrome. Data are from a decision-analysis model which calculated the incremental cost-effectiveness ratios (ICERs) of treatment and prevention of these conditions with rasburicase in adult and paediatric patients (pts) with acute lymphocytic leukaemia (ALL), acute myeloid leukaemia (AML) or non-Hodgkin's lymphoma (NHL) in four European countries[24]

Country	ICER per life-year saved (€)					
	Adult pts			Paediatric pts		
	ALL	AML	NHL	ALL	AML	NHL
Prevention						
Belgium	32 126	101 734	41 383	1 790	3 054	1 710
The Netherlands	31 014	98 210	39 950	1 610	2 748	1 538
Spain	31 496	99 738	40 571	1 688	2 880	1 613
UK	23 794	75 348	30 650	445	760	425
Treatment						
Belgium	1 599	5 062	2 059	NR	NR	NR
The Netherlands	302	956	389	NR	NR	NR
Spain	930	2 944	1 197	NR	NR	NR
UK	−1 344	−24 033	−9 776	NR	NR	NR

NR = not reported.

tancy of patients and the costs, incidence and percentage of hyperuricaemia or tumour lysis syndrome cases that were avoided with rasburicase treatment.[24] Rasburicase was less cost effective (ICER was higher) when there was a lower incidence of hyperuricaemia or tumour lysis syndrome, shorter life expectancy or a reduction in the cases of hyperuricaemia or tumour lysis syndrome prevented with rasburicase.[24]

7. Dosage and Administration

Intravenous rasburicase is approved in the US and EU for the management of acute hyperuricaemia in paediatric (in the US and EU)[11,12] and adult (in the EU only)[12] patients with haematological malignancies or solid tumours who are at risk of anticancer therapy-induced tumour lysis and elevated plasma uric acid concentrations. The recommended dosages are 0.15 mg/kg once daily in the US[11] and 0.2 mg/kg once daily in the US and EU.[11,12] Rasburicase is administered as a 30-minute intravenous infusion in 50mL of sodium chloride 0.9% solution for a single treatment course of 5 days starting prior to or during chemotherapy;[11,12] in the EU, treatment may be extended to 7 days.[11,12] Administration of multiple courses of rasburicase is not recommended.[11,12]

Because of the potential for the development of severe haemolysis, methaemoglobinaemia and hypersensitivity reactions with rasburicase (section 5), the drug is contraindicated in patients with methaemoglobinaemia, glucose-6-phosphate dehydrogenase deficiency or other metabolic disorders known to cause haemolytic anaemia.[11,12] A specific sample-handling procedure must be followed since rasburicase may degrade uric acid in samples of blood, plasma or serum stored at room temperature, resulting in spuriously low measurements. Local prescribing information should be consulted for information on precautions, warnings and sample-handling requirements.[11,12]

8. Place of Rasburicase in the Management of Anticancer Therapy-Induced Hyperuricaemia

Hyperuricaemia is a defining characteristic of laboratory tumour lysis syndrome, a serious condi-

tion that may develop in response to cytolytic anticancer therapy.[1] It requires prompt and aggressive therapy to prevent the development of clinical tumour lysis syndrome, which is associated with serious clinical outcomes such as acute renal failure, seizures, cardiac arrhythmias and sudden death.[2] Thus, the prophylaxis and treatment of hyperuricaemia form part of the strategy for the management of tumour lysis syndrome, which centres on risk recognition and preventive or early pharmacological treatment.[1]

The identification of patients at risk of developing anticancer therapy-induced hyperuricaemia as part of tumour lysis syndrome is based on analysis of various patient and disease characteristics.[2] It is well established that patients at high risk of developing tumour lysis syndrome are those with highly proliferative haematological malignancies or highly treatment-sensitive neoplasms, which undergo rapid tumour cell lysis in response to anticancer therapy.[2] Tumour lysis syndrome occurred in ≈5% of patients receiving treatment for acute lymphoblastic leukaemia, acute myelogenous leukaemia or non-Hodgkin's lymphoma, according to a recent retrospective review of data from 722 adult and paediatric patients with these malignancies; the incidence of tumour lysis syndrome-related mortality was ≈1% in these patients.[4] Highly proliferative malignancies are generally more prevalent in paediatric than in adult patients[5] and, thus, children may be at a higher risk of developing tumour lysis syndrome than adults.

Current National Comprehensive Cancer Network treatment guidelines recommend prophylactic tumour lysis syndrome therapy in patients receiving anticancer treatment for Burkitt's lymphoma and lymphoblastic lymphoma,[25] and suggest that prophylactic therapy be considered in patients receiving treatment for acute myeloid leukaemia,[26] diffuse large B-cell lymphoma, chronic lymphocyctic leukaemia or small lymphocytic leukaemia;[25] there are currently no specific recommendations on the use of tumour lysis syndrome prophylaxis in patients with acute lymphocytic leukaemia. Retrospective analyses suggest that other factors associated with a high risk of developing tumour lysis syndrome include elevated pretreatment uric acid, creatinine or lactate dehydrogenase levels, a high tumour burden, a high leukocyte count, poor hydration, leukaemia or lymphoma infiltration of the kidney, low urinary flow rate and a urinary uric acid to creatinine ratio of >1.[1,2,27]

The standard approach to prophylaxis or treatment of tumour lysis syndrome involves antiuricaemic therapy, intensive hydration and urinary alkalinisation.[1] The primary goals of antiuricaemic therapy are to inhibit the formation of uric acid and increase renal clearance of uric acid.[7] The initiation of anticancer therapy may be delayed in patients at high risk of developing tumour lysis syndrome,[6] and dialysis may be required to correct very high plasma uric acid, phosphorous or potassium concentrations.[1,7]

Currently available antiuricaemic agents include allopurinol, which, along with the active metabolite oxipurinol, inhibits xanthine oxidase-mediated formation of uric acid[8] and rasburicase, the first recombinant uricolytic agent, which increases renal clearance of uric acid via conversion to allantoin (section 2). Oral and intravenous allopurinol are approved for use in both adult and paediatric patients in numerous countries worldwide,[8,28] whereas rasburicase is approved for adult patients in the EU and paediatric patients in the EU and US (section 7).[11,12] Intravenous nonrecombinant urate oxidase (Uricozyme®) is also available in some European countries and has the same mechanism of action as rasburicase.[29]

Although there have been no clinical trials to evaluate the effects of any of these antiuricaemic therapies on the clinical endpoints of hyperuricaemia, such as acute renal failure or death, the normalisation of uric acid levels is expected to reduce the risk of development of these potentially life-threatening conditions. A cross-trial comparison, which should be interpreted cautiously, found that the requirement for haemodialysis was lower in patients who received rasburicase or nonrecombinant urate oxidase in clinical or compassionate-use trials (0–3%) than in patients with similar malignancies in other trials who did not receive treatment with these agents (16–25%).[21]

Oral allopurinol is the mainstay of current preventive antiuricaemic therapy; the intravenous formulation is generally used in patients unable to tolerate oral therapy.[6,7,28] Treatment with oral or intravenous allopurinol 200–800 mg/day has been

shown to reduce the serum uric acid concentration in leukaemia and lymphoma patients with or without existing hyperuricaemia.[30] Allopurinol is generally well tolerated, with the majority of adverse effects being of mild to moderate severity and related to allergic or skin reactions.[8,28]

However, an important limitation of allopurinol treatment arises from it's mechanism of action. Unlike rasburicase, allopurinol prevents the formation of new uric acid, but has no effect on existing uric acid.[8,28] Consequently, there may be a delay of up to 3 days before a clinically significant reduction in plasma uric acid concentration is achieved.[5] The optimal time for initiation of allopurinol treatment is, therefore, 24–48 hours prior to the start of anticancer therapy.[28] Allopurinol may not adequately reduce uric acid levels in patients with existing hyperuricaemia;[30] indeed, 43% of 204 adult patients and 12% of 137 paediatric patients with pretreatment hyperuricaemia (serum uric acid >7.0 mg/dL in this study) who received intravenous allopurinol once daily in a compassionate-use programme did not achieve normalisation of serum uric acid concentration.[31] To facilitate the renal excretion of existing uric acid, it is recommended that allopurinol is administered in conjunction with adequate hydration to optimise diuresis and that neutral or slightly alkaline urine is maintained.[28]

Rasburicase, which facilitates the clearance of existing uric acid via conversion to allantoin (section 2), provides rapid correction of hyperuricaemia. At dosages of 0.15 or 0.2 mg/kg once daily, rasburicase prevented or corrected hyperuricaemia within 4 hours in almost all adult and paediatric patients with acute lymphocytic or non-lymphoid leukaemia or non-Hodgkin's lymphoma (section 4.1). The intravenous administration of rasburicase, however, makes it less convenient than orally administered allopurinol.

The significantly greater efficacy and quicker onset of action of rasburicase than allopurinol in paediatric patients (section 4.2.1) suggest that it may be a better option than allopurinol for prevention or correction of hyperuricaemia. Recent US[2] and French[29] recommendations for the management of tumour lysis syndrome suggest that rasburicase rather than allopurinol be administered in patients at high risk of developing this syndrome. Urinary alkalinisation, which is recommended in allopurinol recipients and associated with various deleterious effects, such as an increased risk of calcium/phosphorous precipitation in the kidney,[30] is not required in patients receiving rasburicase.[6] Although no studies have compared the efficacy of rasburicase with that of intravenous allopurinol, the oral and intravenous allopurinol formulations are bioequivalent.[28] The comparative efficacy of rasburicase and allopurinol has not been investigated in adult patients, and further studies would be useful.

The rapid correction of hyperuricaemia with rasburicase may reduce the likelihood of developing serious clinical outcomes associated with hyperuricaemia, such as acute renal failure. It is thought that the rasburicase-mediated reduction in plasma uric acid may result in an improvement in general renal function and, consequently, clearance of serum phosphate is more efficient and the risk of renal impairment due to calcium/phosphorous precipitation is reduced.[12] Indeed, serum phosphorous and creatinine levels were reduced from baseline in rasburicase recipients in a dose-finding trial (section 4.1). Of 143 paediatric patients who, as per the French treatment recommendations, were assessed as being at high-risk of acquiring tumour lysis syndrome and received rasburicase treatment, none developed clinical complications, suggesting that implementation of these treatment recommendations may facilitate effective prevention and treatment of hyperuricaemia.[32]

Therefore, the potential for an improved clinical outcome in rasburicase recipients may lead to reductions in the length and cost of the hospital stay and the need for dialysis, making it a cost effective treatment option.[24] A 3–4 day course of rasburicase was found to be cost effective for the treatment of hyperuricaemia and tumour lysis syndrome in adults and for the prevention of these conditions in children with acute lymphocytic or myeloid leukaemia or non-Hodgkin's lymphoma (section 6). Depending on the malignancy, it was also cost effective for the prevention of these conditions in some adults (section 6).

However, various assumptions made in this model, such as the assumption that rasburicase treatment would result in 100% of tumour lysis syndrome cases being avoided, may have resulted in

over-estimation of the cost effectiveness of rasburicase.[1,2] Moreover, there are limitations inherent in the projection of future outcomes from current data. Further data are required to determine accurately the cost effectiveness of rasburicase and the comparative costs of treatment with rasburicase versus oral and, in particular, intravenous allopurinol, which like rasburicase is associated with a high unit cost.

Intravenous rasburicase is generally well tolerated at the approved dosages, considering the concomitant administration of anticancer therapy and the severity of underlying disease in rasburicase recipients (section 5). A primary consideration with rasburicase administration is the potential for the development of serious adverse events, especially haematological or respiratory events or hypersensitivity reactions, which occurred in ≤5% of rasburicase recipients in clinical trials and the compassionate-use studies (section 5). The accumulation of hydrogen peroxide (section 2) means that patients with glucose-6-phosphate dehydrogenase deficiency or a known history of allergic, haemolytic or methaemoglobinaemia reactions have an increased risk of haemolytic anaemia or methaemoglobinaemia and should not receive rasburicase (section 7). However, no adverse effects are expected to occur as a result of hydrogen peroxide accumulation in subjects with normal levels of glucose-6-phosphate dehydrogenase. Although limited data are available on the toxicity of allantoin, the accumulation of allantoin in rasburicase recipients is not expected to have clinical consequences in patients with renal dysfunction.[12,13]

Rasburicase and oral allopurinol were similarly tolerated in patients aged up to 17 years and, although there are currently no data on the comparative tolerability in adults, the two drugs are likely to be similarly well tolerated in this patient population.[8,28] Although allopurinol is associated with an increased risk of adverse events because of the accumulation of xanthine and hypoxanthine and xanthine,[6] the small number of cases of xanthine nephropathy reported in the literature suggest that it is a rare occurrence.[7] Rasburicase is likely to be at least as well tolerated as nonrecombinant urate oxidase, which is associated with a similar incidence of serious adverse events (≈5%)[7] as rasburicase (section 5). Rasburicase is less heterogeneous than nonrecombinant urate oxidase and has ≈50% greater specificity for conversion of uric acid to allantoin;[13] however, no comparative studies have been conducted to date and cross-trial comparisons should be made with caution.

The formation of anti-rasburicase antibodies, which occurred in 11% of rasburicase recipients in clinical trials (section 2), may increase the risk of hypersensitivity reactions in patients who receive multiple rasburicase doses. Adverse events associated with allergic reactions occurred in 11% (8 of 71) of patients who received more than one course of rasburicase treatment in the European arm of the compassionate-use trial.[21] It is not yet clear whether antibody formation affects the efficacy of rasburicase; a response to rasburicase treatment was maintained by all but one of the 71 patients who received multiple rasburicase treatment courses.[21] However, multiple courses of rasburicase treatment are not recommended; treatment should be restricted to a single course with a maximum duration of 5–7 days (section 7). Studies investigating the potential correlation between antibody formation and allergic reactions and therapeutic efficacy are ongoing.[6]

The lack of clinically significant drug interactions with rasburicase may offer an advantage over allopurinol, which is associated with several potential drug interactions that may necessitate dosage adjustments when it is coadministered with some other agents.[8,28] A particular consideration with allopurinol is the inhibition of the metabolism of the cytolytic agents mercaptopurine and azathioprine.[6] Rasburicase does not appear to interact with other anticancer drugs (section 2) or drugs metabolised by the hepatic CYP isoenzymes (section 3.2) and, unlike allopurinol, the rasburicase dosage does not require adjustment in patients with renal impairment.[28]

To date, there have been no studies in patients receiving sequential treatment with rasburicase and allopurinol. While concomitant use of the two agents would negate the effect of rasburicase because of allopurinol-mediated inhibition of uric acid production,[6] it is possible that the sequential use of rasburicase followed by allopurinol may allow a shorter course of rasburicase treatment to be administered, resulting in cost savings.[6] It would be interesting to evaluate the therapeutic efficacy and cost

effectiveness of antiuricaemic prevention or treatment with sequential rasburicase and allopurinol.

In conclusion, intravenous rasburicase is effective and generally well tolerated in adult and paediatric patients with, or at risk of developing, anticancer therapy-induced hyperuricaemia. Rasburicase is associated with potentially serious haematological adverse events and hypersensitivity reactions, which must be considered prior to and during administration; it is contraindicated in patients predisposed to haemolysis or methaemoglobinaemia or with glucose-6-phosphate dehydrogenase deficiency. Unlike allopurinol, rasburicase acts on existing uric acid concentrations. Rasburicase treatment resulted in significantly less systemic exposure to uric acid and a quicker therapeutic response than allopurinol in paediatric patients; further studies are needed to determine the comparative efficacy and tolerability of rasburicase and allopurinol in adult patients. Although further pharmacoeconomic data would be useful, rasburicase was most cost effective for the prevention of hyperuricaemia in children and for treatment of this condition in adults. Thus, rasburicase is a useful option for the prophylaxis or treatment of anticancer therapy-induced hyperuricaemia in both adult and paediatric patients.

Disclosure

During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

References

1. McGraw-Hill's access medicine: Harrison's online [online]. Available from URL: http://www.accessmedicine.com [Accessed 2005 Nov 22]
2. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol 2004 Oct; 127 (1): 3-11
3. Pui CH. Rasburicase: a potent uricolytic agent. Expert Opin Pharmacother 2002 Apr; 3 (4): 433-42
4. Annemans L, Moeremans K, Lamotte M, et al. Incidence, medical resource utilisation and costs of hyperuricaemia and tumour lysis syndrome in patients with acute leukaemia and non-Hodgkin's lymphoma in four European countries. Leuk Lymphoma 2003; 44 (1): 77-83
5. Bickert B, Reilly A. Pediatric tumor lysis syndrome. J Pharm Pract 2004; 17 (6): 447-54
6. Jeha S, Pui CH. Recombinant urate oxidase (rasburicase) in the prophylaxis and treatment of tumor lysis syndrome. Contrib Nephrol 2005; 147: 69-79
7. Davidson MB, Thakkar S, Hix JK, et al. Pathophysiology, clinical consequences, and treatment of tumor lysis syndrome. Am J Med 2004 Apr 15; 116 (8): 546-54
8. GlaxoSmithKline UK. Zyloric® (allopurinol) tablets 100mg, 300mg [online]. Available from URL: http://www.emc.medicines.org.uk [Accessed 2005 Nov 24]
9. Pea F. Pharmacology of drugs for hyperuricemia: mechanisms, kinetics and interactions. Contrib Nephrol 2005; 147: 35-46
10. Jacob F, Drelon E, Neefe J, et al. New drug to lower uric acid levels in healthy volunteers: advances on prevention and control of hyperuricemia in malignancies? [abstract no. 1464]. 87th Annual Meeting of the American Association for Cancer Research; 1996 Apr 20-24; Washington, DC, 214
11. Sanofi-Synthelabo Inc. Elitek® (rasburicase) prescribing information [online]. Available from URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda [Accessed 2005 Nov 8]
12. Sanofi-Synthelabo. Summary of product characteristics: Fasturtec® (rasburicase) [online]. Available from URL: http://www.emea.eu.int/humandocs/PDFs/EPAR/fasturtec/H-331-PI-en.pdf [Accessed 2005 Nov 8]
13. European Medicines Agency. Scientific discussion [online]. Available from URL: http://www.emea.eu.int/index/indexh1.htm [Accessed 2005 Nov 18]
14. Cheson BD, Dutcher BS. Managing malignancy-associated hyperuricemia with rasburicase. J Support Oncol 2005; 3 (2): 117-24
15. Pui CH, Mahmoud HH, Wiley JM, et al. Recombinant urate oxidase for the prophylaxis or treatment of hyperuricemia in patients with leukemia or lymphoma. J Clin Oncol 2001 Feb 1; 19 (3): 697-704
16. Lascombes F, Sommelet D, Gebhard F, et al. High efficacy of recombinant urate oxidase in prevention of renal failure related to tumor lysis syndrome (TLS) [abstract no. 4019]. Blood 1998 Nov 15; 92 Suppl. 1 (2): 237b
17. Mahmoud HH, Czerniak R, Auvrignon A, et al. Pharmacokinetics of recombinant urate oxidase SR29142 and anti-SR29142 antibodies in patients with cancer [abstract no. O-145]. Med Pediatr Oncol 1998 Oct; 31: 230
18. Goldman SC, Holcenberg JS, Finklestein JZ, et al. A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. Blood 2001 May 15; 97 (10): 2998-3003
19. Coiffier B, Mounier N, Bologna S, et al. Efficacy and safety of rasburicase (recombinant urate oxidase) for the prevention and treatment of hyperuricemia during induction chemotherapy of aggressive non-Hodgkin's lymphoma: results of the GRAAL1 (Groupe d'Etude des Lymphomes de l'Adulte trial on Rasburicase Activity in Adult Lymphoma) study. J Clin Oncol 2003 Dec 1; 21 (23): 4402-6
20. Wang LY, Shih LY, Chang H, et al. Recombinant urate oxidase (rasburicase) for the prevention and treatment of tumor lysis syndrome in patients with hematologic malignancies. Acta Haematol 2006; 115 (1-2): 35-8
21. Jeha S, Kantarjian H, Irwin D, et al. Efficacy and safety of rasburicase, a recombinant urate oxidase (Elitek®), in the management of malignancy-associated hyperuricemia in pediatric and adult patients: final results of a multicenter compassionate use trial. Leukemia 2005 Jan; 19 (1): 34-8
22. Bosly A, Pinkerton CR, McCowage G, et al. Recombinant urate oxidase (rasburicase) is safe and effective in managing hyperuricemia in children and adults: results of a multi-national compassionate use trial. Blood 2002 Nov 16; 100 (Part 1): 556-7
23. Shin HY, Kang HJ, Park ES, et al. Recombinant urate oxidase (rasburicase) for the treatment of hyperuricemia in pediatric patients with hematologic malignancies: results of a compassionate prospective multicenter study in Korea. Pediatr Blood Cancer 2005 Aug 25

24. Annemans L, Moeremans K, Lamotte M, et al. Pan-European multicentre economic evaluation of recombinant urate oxidase (rasburicase) in prevention and treatment of hyperuricaemia and tumour lysis syndrome in haematological cancer patients. Support Care Cancer 2003 Apr; 11 (4): 249-57
25. National Comprehensive Cancer Network. Practice guidelines in oncology – v.1.2005: non-Hodgkin's lymphoma [online]. Available from URL: http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf [Accessed 2005 Dec 5]
26. National Comprehensive Cancer Network (NCCN). Practice guidelines in oncology – v.1.2006: acute myeloid leukaemia [online]. Available from URL: http://www.nccn.org [Accessed 2005 Nov 24]
27. Montesinos P, Martin G, Perez-Sirvent M, et al. Identification of risk factors for tumour lysis syndrome in patients with acute myeloid leukaemia: development of a prognostic score [abstract no. 1843 plus poster]. American Society of Hematology 47th Annual Meeting; 2005 Dec 10-13; Atlanta (GA)
28. Nabi Biopharmaceuticals. Aloprim® (allopurinol sodium) for injection. Product information [online]. Available from URL: http://www.nabi.com/images/prescribinginfo/aloprim%20PI%202003.pdf [Accessed 2005 Dec 6]
29. Patte C, Sakiroglu C, Ansoborlo S, et al. Urate-oxidase in the prevention and treatment of metabolic complications in patients with B-cell lymphoma and leukemia, treated in the Société Francaise d'Oncologie Pédiatrique LMB89 protocol. Ann Oncol 2002 May; 13 (5): 789-95
30. Holdsworth MT, Nguyen P. Role of i.v. allopurinol and rasburicase in tumor lysis syndrome. Am J Health Syst Pharm 2003 Nov 1; 60 (21): 2213-22, quiz 2223-4
31. Smalley RV, Guaspari A, Haase-Statz S, et al. Allopurinol: intravenous use for prevention and treatment of hyperuricaemia. J Clin Oncol 2000; 18 (8): 1758-63
32. Bertrand Y, Auvrignon A, Nelken B, et al. SFCE (Société Francaise des Cancers de l'Enfant) recommendations for the management of tumour lysis syndrome (TLS): a validation survey [abstract no. 3122 plus poster]. American Society of Hematology 47th Annual Meeting; 2005 Dec 10-13; Atlanta (GA)

Correspondence: *Vicki Oldfield*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 1311, New Zealand.
E-mail: demail@adis.co.nz