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Original Investigation

Rasburicase in Tumor Lysis Syndrome of the Adult: A Systematic Review and Meta-analysis

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Background: The use of rasburicase has been evaluated extensively in children, but not in adults. We review the current literature to evaluate its effect on adults.

Study Design: Systematic review and meta-analysis.

Setting & Population: Adults receiving rasburicase for tumor lysis syndrome (TLS).

Selection Criteria for Studies: Electronic databases, regulatory documents, and websites were searched up to August 7, 2012. Reference lists of published articles were examined for additional relevant references. Any controlled trial or observational studies (controlled before and after) were included. Studies considering children only or mixing data for children and adults were excluded.

Intervention: Rasburicase for TLS.

Outcomes: The primary outcome was TLS development. Secondary outcomes included percentage of patients improving, total adverse events, acute kidney failure, deaths, and serum uric acid and creatinine levels.

Results: 21 studies (24 publications) reported data for 1,261 adult patients, 768 receiving rasburicase for either the treatment or prophylaxis of TLS; these comprised 4 controlled trials and 17 observational studies. No statistically significant differences in clinical TLS development were observed in the controlled trials between the rasburicase and control groups. For the observational studies, 7.4% of patients developed clinical TLS after rasburicase (95% CI, 1.7%-16.7%), 93.4% of patients achieved normalized serum uric acid levels after rasburicase treatment (95% CI, 91.7%-94.6%), 4.4% developed acute kidney injury (95% CI, 3.0%-6.0%), and 2.6% died (95% CI, 0.95%-5.0%). The mean reduction in serum uric acid levels ranged from 5.3-12.8 mg/dL, and for serum creatinine levels, from 0.10-2.1 mg/dL.

Limitations: Controlled trials differed in outcomes reported; meta-analysis was not performed.

Conclusions: Rasburicase is effective in reducing serum uric acid levels in adults with TLS but at a significant cost, and evidence currently is lacking in adults to report whether rasburicase use improves clinical outcomes compared with other alternatives. Until new evidence is available, use of rasburicase may be limited to adult patients with a high risk of TLS.

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INDEX WORDS: Recombinant urate oxidase; nonrecombinant urate oxidase; tumor lysis syndrome (TLS); rasburicase; hyperuricemia; allopurinol; acute kidney injury; outcomes; cost; leukemia; lymphoma.

Tumor lysis syndrome (TLS) is a medical emergency resulting from the rapid release of tumor cell contents into the systemic circulation, leading to the development of potentially life-threatening fluid, electrolyte, and acid-base abnormalities, such as hyperkalemia, hyperphosphatemia, hyperuricemia, and metabolic acidosis. The crystallization of uric acid and calcium phosphate in renal tubules results in tubular obstruction and necrosis, leading to oliguric acute kidney injury, which in turn markedly limits excretion of the toxic metabolites, thus aggravating the fluid, electrolyte, and acid-base abnormalities.[1,2] TLS can occur spontaneously or within 6-72 hours after the initiation of therapy in patients with a large tumor burden or rapidly proliferating tumors, and the severe forms of TLS can be life-threatening. TLS occurs most often in patients with lymphoma or leukemia.[2]

The prevention and successful management of TLS are essential to the success of cancer therapy. Although the clinical manifestation of TLS is complex, with multiple biochemical derangements, hyperuricemia is considered an important player in its pathogenesis. The chemotherapy-induced breakdown of proliferating tumor cells and their nuclei contribute to the increase in uric acid catalyzed by xanthine oxidase. Traditionally, the xanthine oxidase inhibitor allopurinol is used both prophylactically and in the treatment of TLS to suppress serum uric acid levels. Urate oxidase, not normally present in humans, can further degrade uric acid to water-soluble allantoin that is

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excreted freely in urine. Rasburicase is a relatively new form of recombinant urate oxidase. It promptly and effectively degrades uric acid, thus potentially aborting or attenuating hyperuricemia. In children with cancer, rasburicase has been proved effective in the prevention and treatment of TLS.[3] In 2009, the US Food and Drug Administration (FDA) approved the use of rasburicase in adults based on the result of a randomized controlled trial that reported significant improvement in serum uric acid response rates with rasburicase versus allopurinol (87% vs 66%).[4,5] However, higher rates of serious adverse reactions (such as pulmonary hemorrhage, respiratory failure, cardiac [supraventricular] arrhythmias, ischemic coronary artery disorders, and abdominal and gastrointestinal infections) also were reported in patients receiving rasburicase compared to allopurinol.[6,7] Interestingly, but perhaps not surprisingly, no significant difference was observed between groups in the incidence of TLS, suggesting that factors other than high uric acid levels may be important in the causation and perpetuation of TLS.[8] Current published guidelines for the management of TLS in children and adults include the use of rasburicase, especially if hyperuricemia is present despite prophylactic treatment with allopurinol.[8] However, rasburicase can impose a great financial burden, and before recommending the widespread use of rasburicase in adults, there is a need to determine whether clinical outcomes are improved.[6,7] We therefore undertook a systematic review to evaluate the efficacy, effectiveness, and safety of rasburicase in adults to treat or prevent TLS.

METHODS

Study Design

We followed the Cochrane Collaboration methods for conducting this review. We report according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and MOOSE (Meta-analysis of Observational Studies in Epidemiology) statements.[9-11]

Eligibility Criteria

We included any controlled trial (randomized or not) reporting the use of rasburicase for the prevention or management of TLS. In addition, controlled before and after studies were included. We considered data from only published studies in adult patients with any type of cancer for inclusion. Thus, patients younger than 18 years were excluded. Studies reporting data for children and adults were included only if separate data for both populations were provided. All dosages and frequencies of rasburicase were included in this review, and these were considered the active group. We included any type of control interventions (placebo, no treatment, or allopurinol.

Information Sources and Search

Electronic databases including MEDLINE, EMBASE, the Cochrane Library, and Web of Science were searched by an experienced librarian (G.P.) from inception through August 07, 2012, and reference lists of published articles were examined for additional relevant references. The search strategies used for the different databases are shown in Items S1 (provided as online supplementary material). Electronic websites also were searched, including the National Health Service National Research Register, ClinicalTrials.gov, and the FDA. Searches were not restricted by language or study design. Both full-text articles and meeting abstracts were considered for inclusion.

Study Selection and Data Collection

The title and abstract of all citations were screened independently by 2 reviewers (M.A.L.-O. and G.P.) to select potentially relevant studies. Disagreements were resolved by consensus, and any unresolved issues were referred to an adjudicator (A.S.). Data extraction was performed independently by 2 reviewers (M.A.L.-O. and G.P.). We used a standardized extraction form and collected information for the study population, number of centers, types of interventions, primary and secondary outcomes, and analyses reported by the authors.

Outcome Measures

We used different outcome measures for the evaluation of rasburicase as prophylactic or treatment agent. Our primary outcome was the incidence of TLS development as defined by the authors. According to the 2004 Cairo and Bishop[12] definition, TLS can be classified as laboratory or clinical TLS. Laboratory TLS is defined by 2 or more laboratory test result abnormalities occurring within 3 days before or 7 days after chemotherapy (uric acid, >8 mg/dL or 25% increase from baseline; potassium, >6 mmol/L or 25% increase from baseline; phosphorus, >4.5 mg/dL or 25% increase from baseline; and calcium, >7 mg/dL or 25% decrease from baseline). Clinical TLS is defined by the presence of laboratory TLS plus one clinical sign: either creatinine level 1.5 times the upper limit of normal, cardiac arrhythmia/sudden death, or seizure.[1,8,12] Secondary outcomes were percentage of patients achieving serum uric acid levels <6.5 mg/dL, total adverse events, incidence of acute kidney injury, and mortality rate. In addition, we also analyzed mean reductions in serum levels of uric acid and creatinine.

Risk of Bias in Individual Studies

Risk of bias in controlled trials was assessed independently by 2 authors (M.A.L.-O. and G.P.) using the Cochrane Collaboration Risk of Bias tool,[10] in which the internal validity of the studies are judged on the presence or not of selection, performance, detection, attrition, reporting, and other biases. Risk of bias was categorized as low risk, high risk, or unclear (either lack of information or uncertainty over the potential for bias). Observational studies were assessed with a modified version of the Newcastle Ottawa Scale modified for cohort studies without control.[13] We assessed 2 domains: selection (representativeness of the exposed cohort, ascertainment of exposure, and demonstration that the outcome of interest was not present at the start of the study) and outcome (assessment of outcome, follow-up long enough for outcomes to occur, and adequacy of follow-up of cohorts). Possible scores ranged from 0-6, with higher score indicating better quality.

Summary Measures and Synthesis of Results

For studies with comparison groups, dichotomous outcomes were reported as relative risk (RR) and 95% confidence interval (CI). Continuous outcomes were analyzed as mean difference and 95% CI. For laboratory outcomes reported in observational studies, mean differences for pre-post treatment were determined. For clinical outcomes, pooled incidence rates were estimated. We used the Freeman-Tukey arcsine transformation to stabilize variances

and conducted a meta-analysis using inverse variance weights. Then estimates and CI boundaries were back-transformed into proportions. Heterogeneity was quantified by calculating I^2 and reviewing the forest plots examining the overlap of CIs. If CIs do not overlap, it is more likely that the trials are heterogeneous. If heterogeneity was detected ($I^2 > 40\%$), we explored it further using patient and trial characteristics in moderator analyses.[14] All analyses were performed in Comprehensive Meta-Analysis, version 2.2.055 (Biostat Inc), and STATA, version 10 (STATA/IC 10 for Windows, StataCorp LP). Data were not pooled, and we reviewed and summarized the evidence only if insufficient data existed (<2 studies reporting on the same outcome).

RESULTS

Study Selection

Electronic searches retrieved 622 citations from electronic databases, of which 258 were duplicates (Fig 1). We excluded 261 citations based on title or abstract. For the other 103 potentially relevant citations, we retrieved and examined the full text. Twenty-one studies (24 publications) reported data on the use of rasburicase for either the treatment or prophylaxis of TLS.

Study Characteristics

Only 4 studies were controlled trials (5 publications) reporting on 445 patients[5,15-19]: one trial included 3 comparison groups (rasburicase alone, allopurinol alone, and rasburicase combined with allopurinol), 2 trials were dose ranging, and one study compared dose frequency. All included controlled trials evaluated rasburicase as a preventive measure for TLS; no controlled trials evaluated its use for treatment. Studies varied in type of design, quality, and approach. Descriptions of the studies are shown in Table 1. There were 6 prospective observational studies (7 publications) reporting data for 333 patients[20-27] and 11 retrospective studies (12 publications) reporting for 483 patients. Characteristics of observational studies are listed in Tables 2 and 3.

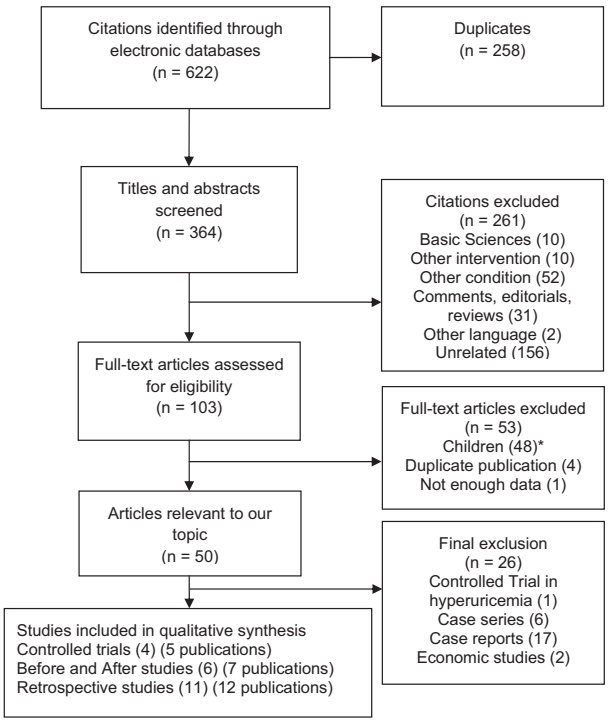

Figure 1. Included studies. *Six studies included children and adults, but data were not provided separately.

Risk of Bias

Efficacy (Controlled Trials)

Three randomized controlled trials[5,16-19] and one nonrandomized historical controlled trial[15] evaluated the efficacy of rasburicase to prevent TLS. Studies were unblinded and none described how random sequence was generated or concealment of allocation was achieved. We judged that there was selective outcome reporting in 3 studies in which only laboratory parameters were evaluated[5,15,16]; only 2 studies reported power calculation.[15-19] Only one study described the analysis based on a modified intent-to-treat population[5] and 2 reported discontinuation rates.[5,16-19] Overall, we judged the risk of bias as high in all controlled trials (Table 1; Table S1).

Effectiveness (Observational Studies)

Most observational studies lacked sufficient power to detect a reduction in clinical or laboratory TLS. Studies were imbalanced, with most reporting fewer high-risk patients. However, in most studies, ascertainment of exposure was through secure records and there was demonstration that the outcome of interest was not present at baseline. Assessment of outcome was performed through record linkage; we judged follow-up to be sufficient for outcomes to occur (Tables 2 and 3; Table S1).

Results of Individual Studies

Controlled Trials

For controlled trials, results of laboratory parameters for all comparisons are listed in Table 4. In one study, rasburicase alone was compared with allopurinol alone and with rasburicase combined with allopurinol.[5] There were no differences in the incidence of clinical TLS between rasburicase alone and allopurinol alone at 35 days (RR, 0.74; 95% CI, 0.17-3.2). Similarly, there were no statistically significant differences between rasburicase alone and combined allopurinol/rasburicase (RR, 1.0; 95% CI, 0.42-2.4) or between allopurinol alone and combined allopurinol/rasburicase (RR, 1.3; 95% CI, 0.3-5.9). Patients in the rasburicase-alone group were less likely to have laboratory TLS (RR, 0.51; 95% CI, 0.32-0.81). There was

Table 1. Characteristics of Included Clinical Controlled Studies

	Methods		Participants		Interventions			Outcomes		
Study	Design, Country	Treatment Duration; Follow-up	Inclusion Criteria	Exclusion Criteria	Intervention	Comparison	Cointerventions	Primary	Secondary	Risk of Bias
Reeves[15] (2008)	CT, US[a]	Single dose; 24 h	Received single dose of rasburicase 0.15 mg/kg to reduce or prevent elevated uric acid levels associated with cancer/ chemotherapy	Age <18 y; <50 kg; pregnancy	Rasburicase 7.5 mg, single dose (n = 17)	Rasburicase 0.15 mg/kg, single dose (n = 23)	Standard therapies to prevent or treat TLS	Normalization of UALs to <8 mg/dL	UALs; % reduction of UALs; no. of patients requiring additional doses; changes in kidney function; costs	High
Ishizawa[16] (2009)	RCT, JP	5 d; 36 d	Adults (18-74 y) at high or potential risk for TLS; estimated life expectancy ≥40 d; ECOG 0-3	Prior allopurinol within 72 h; scheduled to receive asparaginase; allergic reactions; asthma; G6PD deficiency; pregnant or lactating	Rasburicase 0.15 mg/kg, once daily for 5 consecutive d (n = 25)	Rasburicase 0.20 mg/kg, once daily for 5 consecutive d (n = 25)	Chemotherapy	Normalization of UALs	Rate of UAL decline; urinary allantoin levels & excretion rate; kidney function (serum Cr, CCr, K and P or Ca levels), AEs	High
Cortes[5] (2010)	RCT, US	7 d; 52 wk	High or potential risk for TLS; age ≥18 y; ECOG 0-3; life expectancy >3 mo; active leukemia/ lymphoma	Asthma; atopic allergy; hypersensitivity to the drug; G6PD deficiency; uricolytic therapy; relapsed or refractory malignancy	(1) Rasburicase (0.2 mg/kg/d) for 5 d (n = 92); (2) rasburicase (0.2 mg/kg/d) for 3 d then allopurinol (300 mg/d) (n = 92)	Allopurinol (300 mg/d) for 5 d (n = 91)	None	Change in UALs	Hematologic and clinical chemistry; antirasburicase Abs; AEs	High
Vadhan-Raj[17-19] (2009, 2010, & 2011)	RCT, US	5 d; 5 d	Hematologic malignancies; ECOG 0-3; life expectancy >3 mo; high or potential risk for TLS	Asthma; severe allergy; G6PD deficiency; use of allopurinol within 72 h	Rasburicase, single dose, as needed (max 5 doses over 5 d) (n = 40)	Rasburicase 0.15-0.20 mg/ kg IV for 5 d (n = 40)	Chemotherapy	Plasma UA response rate	Plasma UA exposure; no. of doses required to maintain normal UAL; decreased kidney function; electrolyte abnormalities, clinical safety	High

Abbreviations: Abs, antibodies; AE, adverse event; Ca, calcium; CCr, creatinine clearance; Cr, creatinine; CT, controlled trial; ECOG, Eastern Cooperative Oncology Group; G6PD, glucose-6-phosphate dehydrogenase; IV, intravenous; JP, Japan; K, potassium; P, phosphorus; RCT, randomized controlled trial; TLS, tumor lysis syndrome; UA, uric acid; UAL, uric acid level; US, United States.

[a]Historical controls → single dose followed by as-needed doses.

Table 2. Characteristics of Before and After Studies

	Methods		Participants		Interventions		Outcomes		
Study	Design, Country	Treatment Duration; Follow-up	Inclusion Criteria	Exclusion Criteria	Intervention	Cointerventions	Primary	Secondary	NOS Score
Lascombe[23] (1998)	Compassionate trial, UK, FR, SE, BE	5-7 d; 7 d	Risk of hyperuricemia with non-Hodgkin lymphoma, ALL, or nonacute lymphoid leukemia	—	Rasburicase 0.15 mg/kg/d (n = 17)		Reduction of plasma UALs	AE; pts requiring dialysis	5
Pui[25,26] (2001) & Jeha[21,22] (2005)	Compassionate trial, US	7 d; 30 d	Patients with cancer; risk of acute hyperuricemia and TLS	Pregnant or lactating; atopic allergy; asthma; hypersensitivity reaction to rasburicase; use of allopurinol	Rasburicase 0.20 mg/kg; median of 3 d of dosing (range 1-7) (n = 72)	Chemotherapy	Laboratory parameters (WBC, LDH, UALs)	AE	5
Bosly[6] (2003)	Compassionate trial, 9 countries	1-7 d; 7 d	Cancer; risk for hyperuricemia	Allergy; asthma; G6PD deficiency; hypersensitivity to urate oxidase or rasburicase	Rasburicase 0.2 mg/kg twice daily for first 72 h (n = 112)		Reduction of plasma UALs	AE; pts requiring HD; treatment duration	5
Coiffier[20] (2003)	Cohort, BE, FR, CH	3-7 d; 4 d for data	Risk of hyperuricemia with >1 of: large tumor volume 5 cm in diameter, LDH level and/or UAL above NLUL, high Cr level, electrolytes	Atopic allergy; asthma; hypersensitivity to urate oxidase; G6PD deficiency	Rasburicase 0.2 mg/kg/d (n = 100)		Control of UALs during induction phase of chemotherapy	Evaluation of the renal protection	5
Pohlreich[24] (2003)	Cohort, Czech Republic	2 d; 2 d	Hematologic malignancy; high risk of TLS	Not reported	Rasburicase 0.2 mg/kg/d (n = 5)	Chemotherapy	Plasma UALs	Pts achieving UALs below reference values; AEs; AKI	5
Wang[27] (2006)	Cohort, TW	2-6 d; 6 d	ALL; high-grade lymphoma; AML, multiple myeloma; hyperuricemia; intention to begin chemotherapy; minimum life expectancy of 3 mo	Previous treatment with hypouricemic; asthma; atopy; G6PD deficiency	Rasburicase 0.2 mg/kg for 1-7 d; median of 4 d of treatment (range 2-6) (n = 27)	Chemotherapy; treatment for hyperphosphatemia	Serum UA; Cr; Ca; P; sodium; K; LDH; CBC	None	5

Abbreviations and definitions: AE, adverse event; AKI, acute kidney injury; ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; BE, Belgium; Ca, calcium; CBC, complete blood cell count; CH, Switzerland; Cr, creatinine; FR, France; G6PD, glucose-6-phosphate dehydrogenase; HD, hemodialysis; K, potassium; LDH, lactate dehydrogenase; NLUL, normal upper limit; NOS, Newcastle-Ottawa Scale (score range, 0 = poor quality to 6 = high quality); P, phosphorus; pts, patients; SE, Sweden; TLS, tumor lysis syndrome; TW, Taiwan; UA, uric acid; UAL, uric acid level; UK, United Kingdom; US, United States; WBC, white blood cell count.

Table 3. Characteristics of Retrospective Observational Studies

Study	Country	Data Source, y	P or RX	Ascertainment of Outcome	Ascertainment of Exposure	Age[a] (y)	Dose/Duration	Outcomes	NOS Score
McDonnell[28,29] (2005, 2006)	US (n = 11)	NR	RX	Chart review	Pharmacy database and cases known to authors	51 (22-69)	6 mg (single dose) + ALLO	UAL	4
Ho[30] (2006)	US (n = 13)	Jan-Mar 2004	P & RX	Chart review	Hospital and/or pharmacy records	59 (25-82)	0.15-0.2 mg/kg, subsequent doses given based on TLS parameters; ALLO was permitted after 24 h	UAL; TLS clinical and laboratory parameters	4
Hutcherson[31] (2006)	US (n = 11)	Feb 2003-Feb 2005	P & RX	Chart review	NR	61.8 (46-75)	0.045-0.1 mg/kg + ALLO 300 mg/d	UAL; normalization of UALs; kidney failure	3
Llinares[32] (2006)	ES (n = 18)	Jul 2002-May 2004	P	NR	NR	57 (27-84)	0.2 mg/kg/5 d	UAL	2
Steel[33] (2008)	AU (n = 23)	Feb 2005-Feb 2006	P & RX	Pathology database	Medical and dispensing records	66 (31-89)	Exposed: 0.2 mg/kg/d for 1 d (n = 6); nonexposed: ALLO (n = 17)	Kidney failure; electrolytes; UAL; Ca	4
Chow[34] (2009)	US (n = 32)	Mar 2006-Mar 2009	P	Chart review	NR	NR	Exposed: 6 mg (lower fixed-dose group) (n = 7); nonexposed: 0.15 mg/kg/d for 5 d (weight-based dose group) (n = 25)	Normalization of UAL; laboratory parameters	5
Campara[35] (2009)	US (n = 21)	Jul 2002-Oct 2006	P	EMR	NR	55 ± 19	0.15 mg/kg (single dose) + ALLO	UAL; biochemistry	3
Knoebel[36] (2010)	US (n = 48)	Apr 2007-Sep 2008	P & RX	Chart review	NR	50 (19-82)	0.05 mg/kg, 2nd dose given based on TLS parameters + ALLO	Reduction of UAL	4
Vines[37] (2010)	US (n = 34)	Jul 2008-Feb 2009	RX	Chart review and EMR	Pharmacy database	53 (18-88)	6 mg (single dose) + ALLO	Reduction of UAL; Cr and phosphate levels	4
Yim[38] (2010)	US (n = 25)	Dec 2007-Jun 2010	P & RX	NR	NR	54	4.5 mg (single dose)	UAL; laboratory parameters	3
Trifilio[39,40] (2011)	US (n = 247)	Jun 2003-Jan 2008	P	EMR	Pharmacy database	62 (20-92)	3 mg; subsequent doses were allowed	UAL; Cr	5

Abbreviations: ALLO, allopurinol; AU, Australia; Cr, creatinine; EMR, electronic medical record; ES, Spain; NOS, Newcastle-Ottawa Scale modified for cohort studies without control (score range, 0 = poor quality to 6 = high quality); NR, not reported; P, prophylaxis; RX, treatment; TLS, tumor lysis syndrome; UAL, uric acid level; US, United States.

[a]Age is given as median (range) or mean ± standard deviation.

Table 4. Summary of Findings for Controlled Trials

Study	Patients Reaching NUALs	Hyperuricemia	Hyperphosphatemia	Hypocalcemia	Hyperkalemia	Clinical TLS	Laboratory TLS
Reeves[15] (2008): rasburicase fixed dose 7.5 mg vs 0.15 mg/kg[b]	1.0 (0.91-1.2)	—	—	—	—	—	—
Ishizawa[16] (2009): rasburicase 0.15 mg/kg vs 0.20 mg/kg[b]	1.0 (0.93-1.2)	—	—	—	—	—	—
Cortes[5] (2010)							
Rasburicase alone vs allopurinol[b]	—	0.27 (0.12-0.58)[a]	0.86 (0.65-1.2)	0.65 (0.36-1.2)	1.3 (0.68-2.3)	0.74 (0.17-3.2)	0.51 (0.32-0.81)[a]
Rasburicase alone vs rasburicase + allopurinol[b]	—	0.64 (0.26-1.6)	0.85 (0.65-1.1)	0.88 (0.47-1.7)	1.5 (0.77-2.8)	1.0 (0.21-4.8)	0.76 (0.45-1.3)
Allopurinol alone vs rasburicase + allopurinol[b]	—	2.4 (1.3-4.5)[a]	0.99 (0.77-1.3)	1.4 (0.79-2.4)	1.2 (0.59-2.3)	1.3 (0.31-5.9)	1.5 (0.99-2.3)
Vadhan-Raj[17-19] (2011): rasburicase fixed dose for 5 d vs single dose (as needed)[b]	—	1.2 (0.60-2.3)	1.3 (0.73-2.4)	1.4 (0.97-2.0)	1.0 (0.07-15.4)	0.14 (0.01-2.7)	1.3 (0.66-2.5)

Note: Values shown are effect estimates (95% confidence interval); effect estimate is RR. For RR = 1, both groups are equally likely to present/achieve the outcome after therapy; for RR <1, patients in the intervention group are less likely to present the outcome after therapy compared to the control group (protector); and for RR >1, patients in the intervention group are more likely to present the outcome after therapy compared to the control group.

Abbreviations: NUALs, normal uric acid levels; RR, relative risk; TLS, tumor lysis syndrome.

[a]Statistically significant ($P < 0.05$).

[b]Used as control group in the analysis.

a trend of increased laboratory TLS incidence in patients taking allopurinol alone compared with patients allocated to the combined allopurinol/rasburicase group (RR, 1.5; 95% CI, 0.99-2.3). No differences were observed between rasburicase alone and combined allopurinol/rasburicase.

A second randomized controlled trial compared the effects of a single dose of rasburicase followed by as-needed dosing to the standard fixed dosing.[17-19] After 6 days of treatment, patients in the standard-dosing group were 1.1 times more likely to demonstrate normal plasma uric acid levels than the single-dose group (95% CI, 1.0-1.4). When patients were divided by risk level, those at high risk of developing TLS were less likely to respond to a single dose than those at potential risk (RR, 0.72; 95% CI, 0.55-0.96). No differences were found in the incidence of clinical and/or laboratory TLS between patients with a single dose plus as-needed dosing and the fixed dosing. Risks for individual laboratory parameters were classified as: (1) high (serum uric acid >7.5 mg/dL or highly aggressive lymphoma) and (2) potential (highly aggressive lymphoma or lactate dehydrogenase level >2 times upper limit of normal, stage III-IV disease, or stage I-II disease with at least one lymph node/tumor mass >5 cm in diameter).

The third randomized controlled trial was a dose-ranging study.[16] No differences were observed between the rasburicase 0.15-mg/kg and 0.20-mg/kg groups.

In the only nonrandomized historical controlled trial, rasburicase, 0.15 mg/kg, was compared with a single fixed dose of 7.5 mg.[15] There were no differences in the percentage of patients with normal uric acid levels after 24 hours between groups (RR, 0.95; 95% CI, 0.82-1.1). The number of patients requiring a second dose was higher in the 0.15-mg/kg group, but this difference was not statistically significant (RR, 3.7; 95% CI, 0.47-28.8). No differences were observed in mean uric acid or creatinine levels between groups ($P = 0.7$ and $P = 0.5$, respectively).

Observational Studies

For observational studies, results are listed in Table 5.

Primary outcome. Three studies reported TLS development after treatment with rasburicase.[30-32] The pooled incidence rate was 7.4% (95% CI, 1.7%-16.7%).

Secondary outcomes. Ninety-three percent of people (95% CI, 92%-95%) included in the prospective observational studies responded to treatment (normalization of uric acid levels <7.5 mg/dL). Two retrospec-

Table 5. Summary of Findings for Observational Studies by Outcome

Study	Design	No. of Events	N	SE (95% CI)[b]	Estimate (95% CI)[c]
Tumor Lysis Syndrome Development (event rate)					
Ho[30] (2006)	Retrospective	4	13	1.2 (0.68 to 1.70)	0.32 (0.11 to 0.58)
Hutcherson[31] (2006)	Retrospective	0	11	0.29 (−0.27 to 0.86)	0.02 (0.02 to 0.17)
Llinares[32] (2006)	Retrospective	0	18	0.23 (−0.22 to 0.68)	0.01 (0.01 to 0.11)
Pooled[a]				0.55 (0.26 to 0.84)	0.07 (0.02 to 0.17)
Response in Uric Acid Level (event rate)					
Lascombes[23] (1998)	Prospective	17	17	2.9 (2.4 to 3.4)	0.99 (0.88 to 0.99)
Pui[25,26] (2001) & Jeha[21,22] (2005)	Prospective	212	212	3.1 (2.9 to 3.2)	1.00 (0.99 to 1.00)
Bosly[6] (2003)	Prospective	97	97	3.0 (2.8 to 3.2)	1.00 (0.98 to 1.00)
Coiffier[20] (2003)	Prospective	95	100	2.7 (2.5 to 2.9)	0.95 (0.89 to 0.98)
Pohlreich[24] (2003)	Prospective	5	5	2.7 (1.9 to 3.5)	0.96 (0.67 to 0.96)
Wang[27] (2006)	Prospective	27	27	3.0 (2.6 to 3.3)	0.99 (0.92 to 0.99)
Ho[30] (2006)	Retrospective	13	13	2.9 (2.3 to 3.4)	0.98 (0.85 to 0.98)
Hutcherson[31] (2006)	Retrospective	11	11	2.8 (2.3 to 3.4)	0.98 (0.83 to 0.98)
Llinares[32] (2006)	Retrospective	18	18	2.9 (2.5 to 3.4)	0.99 (0.89 to 0.99)
Campara[35] (2009)	Retrospective	21	21	2.9 (2.5 to 3.3)	0.99 (0.90 to 0.99)
Knoebel[36] (2010)	Retrospective	40	48	2.3 (2.0 to 2.6)	0.83 (0.71 to 0.92)
Vines[37] (2010)	Retrospective	28	34	2.3 (1.9 to 2.6)	0.81 (0.67 to 0.92)
Yim[38] (2010)	Retrospective	23	25	2.5 (2.1 to 2.9)	0.90 (0.77 to 0.99)
Trifilio[39] (2011)	Retrospective	175	247	2.0 (1.9 to 2.1)	0.71 (0.65 to 0.76)
Steel[33] (2008)	Retrospective	6	6	2.8 (2.0 to 3.5)	0.96 (0.71 to 0.97)
Chow[34] (2009)	Retrospective	32	32	3.0 (2.6 to 3.3)	0.99 (0.93 to 0.99)
Pooled[a]				2.6 (2.6 to 2.7)	0.93 (0.92 to 0.95)
Total Adverse Events (event rate)					
Pui[25,26] (2001) & Jeha[21,22] (2005)	Prospective	18	387	0.4 (0.34 to 0.54)	0.05 (0.03 to 0.07)
Coiffier[20] (2003)	Prospective	4	100	0.43 (0.23 to 0.62)	0.04 (0.01 to 0.09)
Pohlreich[24] (2003)	Prospective	0	5	0.42 (−0.38 to 1.20)	0.04 (0.04 to 0.33)
Wang[27] (2006)	Prospective	1	27	0.46 (0.09 to 0.83)	0.05 (0.00 to 0.16)
Ho[30] (2006)	Retrospective	0	13	0.27 (−0.25 to 0.79)	0.02 (0.02 to 0.15)
Hutcherson[31] (2006)	Retrospective	0	11	0.29 (−0.27 to 0.86)	0.02 (0.02 to 0.17)
Llinares[32] (2006)	Retrospective	0	18	0.23 (−0.22 to 0.68)	0.01 (0.01 to 0.11)
Campara[35] (2009)	Retrospective	0	21	0.22 (−0.20 to 0.63)	0.01 (0.01 to 0.10)
Trifilio[40] (2011)	Retrospective	1	287	0.14 (0.03 to 0.26)	0.01 (0.00 to 0.02)
Steel[33] (2008)	Retrospective	0	6	0.39 (−0.35 to 1.10)	0.04 (0.03 to 0.29)
Pooled				0.33 (0.26 to 0.39)	0.03 (0.02 to 0.04)
Acute Kidney Injury (event rate)					
Lascombes[23] (1998)	Prospective	1	17	0.58 (0.12 to 1.00)	0.08 (0.00 to 0.25)
Pui[25,26] (2001) & Jeha[21,22] (2005)	Prospective	28	387	0.55 (0.45 to 0.65)	0.07 (0.05 to 0.10)
Bosly[6] (2003)	Prospective	1	97	0.25 (0.05 to 0.44)	0.01 (0.00 to 0.05)
Coiffier[20] (2003)	Prospective	0	100	0.1 (−0.10 to 0.30)	0.00 (0.00 to 0.02)
Pohlreich[24] (2003)	Prospective	0	5	0.42 (−0.38 to 1.20)	0.04 (0.04 to 0.33)
Wang[27] (2006)	Prospective	0	27	0.19 (−0.18 to 0.56)	0.01 (0.01 to 0.08)
Ho[30] (2006)	Retrospective	0	13	0.27 (−0.25 to 0.79)	0.02 (0.02 to 0.15)
Hutcherson[31] (2006)	Retrospective	0	11	0.29 (−0.27 to 0.86)	0.02 (0.02 to 0.17)
Llinares[32] (2006)	Retrospective	1	18	0.56 (0.11 to 1.00)	0.08 (0.00 to 0.23)
Campara[35] (2009)	Retrospective	2	21	0.69 (0.27 to 1.10)	0.11 (0.02 to 0.27)
Steel[33] (2008)	Retrospective	0	6	0.39 (−0.35 to 1.13)	0.04 (0.03 to 0.29)
Pooled				0.42 (0.35 to 0.50)	0.04 (0.03 to 0.06)

(Continued)

Table 5 (Cont'd). Summary of Findings for Observational Studies by Outcome

Study	Design	No. of Events	N	SE (95% CI)[b]	Estimate (95% CI)[c]
		Deaths (event rate)			
Pui[25,26] (2001) & Jeha[21,22] (2005)	Prospective	4	20	0.96 (0.53 to 1.40)	0.21 (0.07 to 0.41)
Coiffier[20] (2003)	Prospective	0	100	0.10 (−0.10 to 0.30)	0.00 (0.00 to 0.02)
Pohlreich[24] (2003)	Prospective	0	5	0.42 (−0.38 to 1.20)	0.04 (0.04 to 0.33)
Wang[27] (2006)	Prospective	0	27	0.19 (−0.18 to 0.56)	0.01 (0.01 to 0.08)
Ho[30] (2006)	Retrospective	0	13	0.27 (−0.25 to 0.79)	0.02 (0.02 to 0.15)
Hutcherson[31] (2006)	Retrospective	0	11	0.29 (−0.27 to 0.86)	0.02 (0.02 to 0.17)
Llinares[32] (2006)	Retrospective	0	18	0.23 (−0.22 to 0.68)	0.01 (0.01 to 0.11)
Campara[35] (2009)	Retrospective	3	21	0.82 (0.40 to 1.20)	0.16 (0.04 to 0.34)
Steel[33] (2008)	Retrospective	1	6	0.95 (0.21 to 1.70)	0.21 (0.01 to 0.56)
Pooled				0.32 (0.20 to 0.45)	0.03 (0.01 to 0.05)
		Creatinine Levels (mean difference, post- vs pretreatment)			
Coiffier[20] (2003)	Prospective	—	100		−0.23 (−1.10 to 0.60))
Hutcherson[31] (2006)	Retrospective	—	11		−2.1 (−2.8 to −1.4)
Campara[35] (2009)	Retrospective	—	21		0.18 (−0.05 to 0.40)
Knoebel[36] (2010)	Retrospective	—	48		−0.10 (−0.39 to 0.19)
Vines[37] (2010)	Retrospective	—	34		−0.80 (−1.30 to −0.32)
Yim[38] (2010)	Retrospective	—	25		−0.20 (−0.77 to 0.37)
		Uric Acid Levels (mean difference, post- vs pretreatment)			
Bosly[6] (2003)	Prospective	—	97		−12.8 (−20.2 to −5.4)
Coiffier[20] (2003)	Prospective	—	11		−9.4 (−13.4 to −5.4)
Pui[25,26] (2001) & Jeha[21,22] (2005)	Prospective	—	212		−10.1 (−16.0 to −4.2)
Wang[27] (2005)	Prospective	—	27		−10.3 (−15.7 to −4.9)
Ho[30] (2006)	Retrospective	—	13		−8.4 (−12.2 to −4.6)
Hutcherson[31] (2006)	Retrospective	—	11		−10.2 (−13.4 to −7.0)
Llinares[32] (2006)	Retrospective	—	11		−11.2 (−16.0 to −6.4)
McDonnell[28,29] (2006)	Retrospective	—	11		−7.3 (−9.6 to −5.0)
Campara[35] (2009)	Retrospective	—	21		−7.4 (−12.2 to −2.6)
Knoebel[36] (2010)	Retrospective	—	48		−5.9 (−8.6 to −3.1)
Vines[37] (2010)	Retrospective	—	34		−7.4 (−11.4 to −3.4)
Yim[38] (2010)	Retrospective	—	25		−9.0 (−13.7 to −4.3)
Trifilio[35] (2011)	Retrospective	—	247		−5.3 (−10.6 to −0.03)

Note: Analysis was performed with a fixed-effect model unless otherwise stated.
Abbreviations: CI, confidence interval; SE, standard error.
[a]Random effects model was used ($I^2 > 40\%$).
[b]Variance stabilizing transformation.
[c]Estimates are proportions for dichotomous outcomes and mean difference for continuous outcomes.

tive studies found that the determinants associated with poor response to a single low dose of rasburicase were high uric acid level[36,39] and white blood cell count at baseline.[36] Total adverse events were reported in 2.6% (95% CI, 1.7%-3.8%) of patients, 4.4% developed acute kidney injury (95% CI, 3.0%-6.0%), and 2.6% died (95% CI, 0.9%-5.0%) after receiving rasburicase. The mean reduction of uric acid levels in patients taking rasburicase ranged from 5.3-12.8 mg/dL from baseline to 24-72 hours after treatment. Most studies did not show a statistically significant difference in creatinine levels before and after rasburicase treatment.

Additional Analysis

No significant associations were observed between treatment effect and study design or quality.

DISCUSSION

Our systematic review of the literature to evaluate the efficacy, effectiveness, and safety of rasburicase in adults demonstrates that it is effective in reducing serum uric acid levels in adults with TLS. In the included observational studies, rasburicase reduced mean uric acid levels by 5.3-12.8 mg/dL from baseline in 24-72 hours after treatment. However, random-

ized controlled data are lacking for adults to suggest whether use of rasburicase improves clinically relevant outcomes compared to less costly alternatives. Currently in the literature there are only 4 controlled trials, with no similar outcomes to pool treatment effects. Although uncontrolled longitudinal studies could be at greater risk of bias, they may be acceptable for evaluating some events when better evidence is lacking.

Urate oxidase (recombinant and nonrecombinant) use is prominent in current management practice, with a widely held belief that it is the best alternative. However, data regarding its efficacy are limited; most studies evaluating its effectiveness have been small and focused on prevention, making it difficult to generalize results for management. To our knowledge, this is the first systematic review summarizing the available evidence on the use of rasburicase for the prevention or treatment of TLS in adults. We observed that the main advantage for its use is the rapid onset of action and rapid decrease in uric acid levels. Results from uncontrolled studies in adults are consistent with results seen in children[3]; 99% of patients on a dose of 0.15-0.2 mg/kg can achieve an 88% reduction in uric acid levels.[4,41] Most published case reports (74%) treating adults with rasburicase/urate oxidase for TLS showed an improvement in uric acid levels or kidney function. However, there is little evidence from controlled trials supporting its efficacy in improving outcomes in adult patients.

Our analysis also affirms the general limitations of meta-analyses, as discussed next. First, we are constrained to the available evidence reported by the authors, and the strength of our results is tempered by the quality of the body of published works. Second, the total number of patients for our primary endpoint and laboratory outcomes was small even after pooling, which led to wide CIs in some instances. Third, publication bias is a frequent problem of meta-analysis that can be further complicated by differences on the individual studies identified. Furthermore, there was moderate heterogeneity across studies, which may indicate that the dispersion of event rates is associated with differences in study characteristics. For these reasons, our results from observational studies should be interpreted recognizing the limitations of meta-analysis as a statistical technique. Fourth, for controlled trials, no attempts were made to perform a meta-analysis. We summarized the evidence by the clinical question they answered.[5,15,16-19] In addition, trials reported group imbalances that could be associated with overestimates of effect.[10] Fifth, several studies were sponsored by the manufacturer of the drug. Studies sponsored by pharmaceutical companies have been linked to tendentious reporting of outcomes that favors the sponsor.[42]

Based on the present evidence, the potential clinical benefits of urate oxidase (nonrecombinant or recombinant) in adults with malignancy cannot be ruled out, particularly given the effectiveness shown in lowering serum uric acid levels, which is an important proxy for outcome. The other alternative, allopurinol, an xanthine oxidase inhibitor, requires up to 72 hours to inhibit de novo generation of uric acid without substantially decreasing existing uric acid excess.[5] In contrast, rasburicase is capable not only of preventing hyperuricemia, but also quickly reversing it. Nonetheless, the management of TLS involves a multifaceted approach, requiring not only the reduction and constant monitoring of uric acid levels, but also the management of other metabolic abnormalities. Rasburicase has not shown benefit in the treatment of hyperkalemia, hyperphosphatemia, hypocalcemia or creatinine levels. Therefore, its use in the treatment of TLS should be carefully individualized and take into consideration that the cost-effectiveness ratio has been reported to range from $27,982.77-$119,643.59 per life-year.[43] This upper limit is greater than the $50,000 per quality-adjusted life-year threshold proposed to assess the cost-effectiveness of an intervention.[44] However, further studies with improved methodological approaches are needed to evaluate the efficacy, safety, and cost-effectiveness of rasburicase in the treatment of patients with TLS.

In conclusion, rasburicase is effective in suppressing hyperuricemia in adults during the treatment or prophylaxis of tumor lysis, but is costly and has serious potential side effects. Currently available studies lack appropriate controls or clinically relevant end points to determine whether rasburicase therapy improves clinical outcomes. Thus, until more evidence becomes available, use of rasburicase should be limited to patients with high risk of TLS.

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SUPPLEMENTARY MATERIAL

Table S1: Risk of bias scores for the included studies.

Item S1: Search strategies.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2013.02.378) is available at www.ajkd.org.

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