Efficacy and cost of single-dose rasburicase in prevention and treatment of adult tumour lysis syndrome: a meta-analysis

Feng X, Dong K, Pence S, Inciardi J, Bhatada NS

CRD summary
This poorly reported review concluded that single-dose rasburicase was clinically effective and cost efficient for the prophylaxis of high-risk tumour lysis syndrome and treatment of hyperuricaemia in adult cancer patients. It is unclear whether these conclusions are supported by the small and potentially unreliable evidence base.

Authors’ objectives
To compare the efficacy and cost of single-dose rasburicase versus daily dose for five days or treatment with allopurinol in adult cancer patients with hyperuricaemia or high risk of tumour lysis syndrome.

Searching
Major databases and hosts were searched (including PubMed and Science Direct to May 2012). Prescribing information, practice guidelines and US Food and Drug Administration reviews on allopurinol and rasburicase were reviewed. Clinical trials were searched for via ClinicalTrials.gov. Only studies in English were considered for inclusion.

Study selection
Randomised controlled trials (RCTs), prospective cohort studies, case-control studies and case series that focused on the use of single-dose rasburicase in adult patients with cancer were considered for inclusion. Treatment focus was the prophylaxis of high-risk tumour lysis syndrome and treatment of hyperuricaemia. Studies appeared to be required to report response rates and time-dependent plasma uric acid reduction.

Studies were conducted in USA, Singapore, Australia and Spain. Mean ages of participants ranged from 33 to 66 years. Diagnoses included various types of leukaemia/lymphoma. Single-dose rasburicase dosage varied from 3mg to 7.5mg as a fixed dose and from 0.05mg/kg to 0.2mg/kg in weight-based dosage. One control group received allopurinol as 300mg for five days. One study arm gave rasburicase for days one to three and allopurinol on days three to five.

It was unclear how many reviewers screened studies for inclusion.

Assessment of study quality
Included studies were not assessed for methodological quality.

Data extraction
Reported response rates and serum uric acid levels were extracted (baseline, 24 hours, 48 hours and 72 hours after treatment). For single-dose studies, participants were classed as responders if they did not need another dose of rasburicase within three days to maintain uric acid level at ≤7.5mg/dL without significant rebound. For all other participants, responders were those who achieved or maintained uric acid level ≤ 7.5mg/dl during days three to seven of treatment. Single-dose rasburicase studies were grouped into lower-dose versus standard-dose. Odds ratios and 95% confidence intervals were calculated for differences in response rates between groups.

It was unclear how many reviewers performed the data extraction.

Methods of synthesis
Pooled single-dose study results were compared with pooled daily dose or pooled allopurinol results; the statistical methods were not clearly reported but it appeared that a weighted mean was calculated. Odds ratios and 95% confidence intervals were presented for plasma uric acid response rates. A timeline analysis showing changes in plasma uric acid over time was reported.

Results of the review
Ten studies were included (eight retrospective and two prospective) with 269 patients treated with single-dose rasburicase. Study designs were not reported clearly but included an RCT and other studies where historical controls were used. Four studies appeared to present comparative data. Two studies reported only median uric acid levels and one further study did not report levels at all of the pre-specified time points.

**Response rate**: The pooled response rate for single-dose rasburicase did not significantly differ from the rate for daily-dose rasburicase. The response rate for single-dose rasburicase was significantly better compared with allopurinol (OR 3.83, 95% CI 2.17 to 6.76). There was no significant difference between prospective versus retrospective single-dose studies in response rates.

**Uric acid timeline analysis**: The pooled single-dose studies effectively controlled plasma uric acid levels below 4mg/dL at all time points. Daily-dose studies had steeper control of plasma uric acid levels compared with single-dose studies or allopurinol. Allopurinol failed to control uric acid levels within 72 hours of treatment.

**Dose analysis**: There was some indication of dose differences in single-dose rasburicase in the control of uric acid levels but these were not statistically significant.

**Cost information**
Direct costs for each treatment regimen were compared against respective response rates from the meta-analysis. The authors stated that standard single-dose rasburicase had non-inferior clinical benefits and significant cost savings compared with daily dosing of rasburicase over five days.

**Authors’ conclusions**
Single-dose rasburicase is clinically effective and cost efficient for the prophylaxis of high-risk tumour lysis syndrome and treatment of hyperuricaemia in adult cancer patients.

**CRD commentary**
This review addressed a clear question with inclusion criteria which partially addressed the topic of interest. Given that the objective was to compare single-dose rasburicase with alternatives, it was unclear why inclusion criteria did not specify comparative studies. Overall, reporting was poor and made it difficult to ascertain whether appropriate methods were used for searches, screening and data extraction or analysis. The exclusion of studies that were not in English and a lack of clarity on the databases searched suggest that relevant studies may not have been considered for inclusion. The primary studies were not assessed for reliability and it was difficult to evaluate them based on the reported information. It was not clear that pooling potentially heterogenous study designs, populations and interventions was appropriate and insufficient information was provided on the statistical analysis to judge its suitability. The cost analysis was limited.

Overall, the authors present strong conclusions that are not supported by the sparse evidence and may not be reliable.

**Implications of the review for practice and research**

**Practice**: The authors stated that lower doses of rasburicase should be cautiously used. Patients with high-risk tumour lysis syndrome should be closely monitored if a lower single-dose of rasburicase were used.

**Research**: The authors stated a need for prospective clinical trials to explore dosage of single-dose rasburicase for the prophylaxis of high-risk tumour lysis syndrome and treatment of hyperuricaemia in adult cancer patients

**Funding**
Not reported.

**Bibliographic details**

**PubMedID**
23550846
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.