Allopurinol for the treatment of chronic kidney disease: a systematic review

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Scientific summary

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Background

The term chronic kidney disease (CKD) is used to describe abnormal kidney function (or structure) and is defined according to the presence or absence of kidney damage and level of kidney function. Traditionally serum creatinine measurements were the mainstay for initial identification of CKD. Higher levels of creatinine indicate a lower glomerular filtration rate (GFR), which indicates decreased renal function. In clinical practice, a calculated estimate of GFR (eGFR) using a formula to identify people with CKD is now preferred.

People with CKD have an increased prevalence of cardiovascular disease (CVD) and are more likely to die from a CVD-related cause than they are to progress to end-stage renal disease. Allopurinol (Zyloric®, Aspen) is a drug commonly used to treat hyperuricaemia in patients with gout. Evidence is emerging that it may also have a role to play in slowing down the progression of CKD and reducing the risk of CVD.

Objectives

The aim of this systematic review was to address the following research question: does allopurinol reduce mortality, the progression of chronic kidney disease or cardiovascular risk in people with CKD? Given the importance of adverse events (AEs) (common and rare), a secondary aim was to consider the evidence from observational studies describing AEs and quality-of-life data.

Methods

The following databases were searched for relevant published literature on 7 January 2013:

- MEDLINE (1946 to 7 January 2013)
- EMBASE (1974 to 28 December 2012)
- The Cochrane Library (Issue 1, 2013)
- ClinicalTrials.gov (7 January 2013).

Search terms included a combination of index terms (for the disease) and free-text words (for the technologies involved). No methodological filters or other limits were employed. In addition, two manufacturers [GlaxoSmithKline who are listed as the manufacturer of Zyloric in *British National Formulary* No. 64 (September 2012) and Aspen who were identified as the current marketing holder of Zyloric by GlaxoSmithKline] were approached for data. A second search was conducted to identify studies of allopurinol-related AEs.

The citations identified by the search strategy were assessed for inclusion through two stages by two independent reviewers (NF and GP). First, all titles and abstracts were screened to identify all potentially relevant citations; and, second, inclusion criteria were applied to full-text articles.

The results of the data extraction and quality assessment for each study were presented in structured tables and as a narrative summary. All summary statistics were extracted for each outcome and, where possible, data were pooled and meta-analysis was carried out using a fixed-effects model and separating outcomes by the time points at which they were reported (6, 9, 12 and 24 months). Mean differences and confidence intervals (CIs) were presented.

Heterogeneity was explored through consideration of the study populations, methods and interventions and by visualisation of results. Heterogeneity was assessed in statistical terms, by the chi-squared test for homogeneity and the I^2 statistic.

Results

Four randomised controlled trials (RCTs) including 257 patients comparing allopurinol with usual care and 21 observational studies including 2372 patients were included in the review of AEs. Efficacy evidence was derived solely from the RCTs, while AE data were derived from RCTs and observational studies. No studies reporting on quality-of-life data were identified.

The RCTs included in the review were of acceptable methodological quality. However, all RCTs were small (varying in size from 40 to 113 patients) and information on randomisation and allocation was, for the most part, lacking. Patients in RCTs received either allopurinol or usual care. A placebo was utilised in only one trial, which was the only trial that was described as double blind.

Observational studies varied in terms of how they were conducted (prospective and retrospective cohort studies, case–control studies and reviews of case reports) and the types of patients included (age, sex, ethnicity, indications for allopurinol, comorbidities and concomitant medications).

Two RCTs included patients with a mean age <43 years, whereas in the other two trials the mean age was >70 years. Three of the four trials included a majority of male patients. While baseline clinical markers were similar in three trials, the mean eGFR was higher and the mean serum creatinine lower in the fourth study, suggesting milder CKD. Baseline diastolic blood pressure was also higher in this fourth study and, unlike the other trials, patients taking angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers were excluded. For these reasons, this trial was excluded from meta-analysis sensitivity analyses.

The length of follow-up in the RCTs ranged from 6 months to a mean of 24 months. This latter trial was the only trial to report any deaths during the follow-up period. Both deaths were in the control arm.

Progression of CKD was measured by eGFR in three trials and by changes in serum creatinine in the remaining study. No significant differences in eGFR over time were reported in any study and no statistically significant differences in eGFR between treatment and control groups were reported in more than one study. One study reported on patients who had stable and worsening of renal function, defined, respectively, as an increase in serum creatinine level at the end of the study by <40% compared with baseline and by >40% compared with baseline, but not yet requiring dialysis. It was reported that significantly more patients in the control group showed deterioration in kidney function at the end of the study (percentage of individuals with stable disease for allopurinol and control were 84% and 54%, whereas for worsening disease they were 12% and 42% respectively; $p=0.015$).

Cardiovascular events were measured in only one trial, in which there were twice as many cardiovascular events in the control arm (27%) as in the allopurinol arm (12%). Kaplan–Meier survival showed that patients in the allopurinol group had a lower cardiovascular risk than patients in the control group (log-rank 4.25; $p=0.039$). No significant differences between groups were reported for blood glucose levels or measures of cholesterol levels or triglyceride in the other three trials. Significant improvements in endothelial function, as measured by flow-mediated dilatation (FMD) and left ventricular mass index (LVMI), were reported in the allopurinol group in one of the studies. The change seen in LVMI was reported to have correlated significantly with the change in FMD. There were no correlations found between uric acid concentration (either its baseline or its change) and the changes seen in LVMI or FMD.

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Changes in mean systolic blood pressure over time were reported in the allopurinol group in one study and in mean arterial pressure in the very small subgroup of patients with normal blood pressure at baseline in the allopurinol group ($n=9$) in another study. Meta-analysis was confined to changes in mean systolic and diastolic blood pressure in three trials. No significant differences between groups were found at any point in time.

Uric acid concentration was measured in all of the included RCTs. Changes over time were reported to be significantly improved in the allopurinol group in all four trials. A meta-analysis confirmed this improvement at 12 months (mean difference between treatment groups, –0.17 mmol/l; 95% CI –0.33 to 0.00 mmol/l), although based on the I^2 test (96%), a large amount of statistical heterogeneity was observed.

Of 21 studies reporting on AEs, 11 reported data on general AEs of any type or severity. Overall, 9.2% of patients reported an AE, most commonly rash and gastrointestinal problems. Two patients (<1%) reported a serious adverse event (SAE) [only known in one case, which was allopurinol hypersensitivity syndrome (AHS)] and no deaths due to AEs were reported in these studies. In a pharmacovigilance study of 10 patients, who were all selected because they had experienced a SAE, there were four instances of AHS and three instances each of acute intestinal nephritis and acute renal failure. Two patients were reported to have died, but it is not reported which SAEs resulted in death.

Severe cutaneous adverse reactions (SCARs) were reported on by eight observational studies. Two studies reported the incidence of SCARs to be 2%. Severe cutaneous adverse reactions typically occurred within the first 2 months of commencing allopurinol. Observational studies also examined the relationship between allopurinol dose and AEs. In two studies examining the relationship with mild AEs, the mean dose was 221–227 mg/day. Mean or median doses in groups of patients experiencing a SCAR varied across seven studies from 100 mg/day to 300 mg/day. Evidence for whether or not AEs and SCARs were dose related was conflicting. In populations of all ethnicities, the *HLA-B*5801* allele was found to be strongly associated with SCARs, particularly in Chinese and Korean populations. Two studies of Singaporean populations also identified impaired renal function to increase the risk of SCARs.

Conclusions

Based on findings from four RCTs, there is limited evidence that allopurinol reduces CKD progression or reduces the incidence of cardiovascular events or the prevalence of cardiovascular risk factors. However, the evidence is derived from a relatively small number of trials with limited numbers of patients, relatively short follow-up and inconsistencies in outcome measures. No evidence for a significant change in blood pressure, a risk factor for both CKD and CVD, was reported from any of the trials or from our meta-analysis. However, this finding may be confounded by other changes in treatment protocols and this requires further investigation.

Based on evidence from RCTs and 21 observational studies, it appears that AEs, and in particular SAEs, attributable to allopurinol are rare. However, the exact incidence is unknown. Based on data extracted from observational studies, it is speculated that the incidence of SCARs may be no more than 2% of patients treated. However, this estimate is derived from evidence of patients treated with allopurinol for any indication and not for CKD. Direct evidence for the impact of allopurinol on quality of life is lacking.

Given the uncertainties in the evidence base highlighted above, there is a need for a further RCT to be conducted, comparing allopurinol with usual care. Ideally, a double-blind trial design should be employed and, hence, usual care will also include a placebo. The dose of allopurinol should be in accordance with guidelines for current practice. Ideally, such a trial should be adequately powered to assess for CKD progression and also to consider stratification of key factors such as age, ethnicity, stage of CKD, comorbidities and concomitant medication (particularly other urate-lowering medications). Given the

chronic nature of the disease, a minimum follow-up period of 24 months is required. As a minimum, end points should include measures of eGFR, cardiovascular events, cardiovascular risk factors and AEs (including SAEs, particularly SCARs). In addition, end points could also include changes in concomitant medication (e.g. antihypertensives) and disease-specific quality-of-life measures. In order to inform analysis, it is important to collect information on the following baseline characteristics: age, sex, ethnicity, comorbidities and concomitant medication. The feasibility of collecting data on other lifestyle factors such as smoking, diet and alcohol intake (which are all cardiovascular risk factors and/or impact on levels of uric acid) should also be considered. Many of these requirements may be met by the ongoing CKD-FIX (Controlled trial of slowing of Kidney Disease progression From the Inhibition of Xanthine oxidase) trial.

Alongside the RCT, additional supporting data are required from observational studies of patients with CKD and using allopurinol. Such studies could collect invaluable data on the relationship between allopurinol and a number of risk factors and outcomes.

Study registration

The study is registered as PROSPERO CRD42013003642.

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