Extended Effects of Allopurinol on Disease Progression in Chronic Kidney Disease of Unknown Aetiology (CKDu) Patients: Two-Year Follow-up of a Randomized Controlled Trial

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CKDu is a significant emerging health challenge in Sri Lanka. Lack of a clear pathogenesis has become a clinical challenge and has prevented development of effective treatment strategies. Among possible interventions, long-term efficacy of urate-lowering therapies like Allopurinol in slowing disease progression remains uncertain. This study aimed to assess whether the extended, two-year urate lowering therapy, following an initial one-year trial, can significantly delay CKDu progression, reduce morbidity and mortality, prevent cardiovascular events (CVE), and improve clinical outcomes. In this open-label, single-centre randomized controlled trial, 335 CKDu patients from the Girandurukotte renal clinic were assigned to either a treatment group (n=165; Allopurinol targeting SUA < 6 mg/dL in males, <5 mg/dL in females) or a control group (n=162; standard care). Patients were followed for two additional years. Primary endpoints were renal progression, assessed via eGFR decline, CVE, and survival. Secondary endpoints included changes in blood pressure, lipid profiles, electrolytes, inflammatory markers (hs-CRP), hematological parameters, and urinary biomarkers. Data were analyzed using linear mixed models (LMM), Kaplan–Meier (KM) survival curves, and Cox regression. At the beginning of the extended follow-up, mean SUA was significantly lower in the treatment compared to controls (5.74 ± 1.42, 6.94 ± 1.36 mg/dL, $p < 0.001$), reflecting the effect of one-year trial. LMM showed significant differences in SUA trends ($p < 0.001$). However, there were no significant differences in eGFR decline over time between groups ($p = 0.943$), and in the rate of decline between groups ($p = 0.461$). Renal event-free survival was higher in the treatment group (98.2% vs. 93.8%; log-rank $p = 0.049$), with a renoprotective trend in Cox analysis (HR = 0.279, $p = 0.053$). Occurrence of CVE was rare ($p = 1.000$) and no significant differences were observed in secondary endpoints (all $p > 0.05$). Although extended allopurinol therapy did not significantly alter CKDu progression or cardiovascular outcomes, it showed sustained changes in SUA and improved renal event-free survival. This study represents a meaningful step forward in CKDu research, highlighting the feasibility and potential benefit of long-term urate-lowering strategies.

Keywords: RCT, CKDu, hyperuricemia, allopurinol, eGFR decline