Randomized Trial of the Effects of Ferric Citrate in Patients with Advanced Chronic Kidney Disease

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INTRODUCTION AND AIMS: We hypothesized that provision of fixed dose ferric citrate to patients with advanced chronic kidney disease, independent of serum phosphate or degree of anemia, would improve multiple biochemical aspects simultaneously and reduce the need for exogenous ESA or intravenous iron.

METHODS: Patients with eGFR &lt;=88/84; 20 ml/min and who were not anticipated to start RRT within 8 weeks were randomized 2:1 to receive fixed dose ferric citrate (FC, 210 mg, two per meal) or standard of care treatment (SOC). 203 patients were randomized and 199 attended at least 1 follow up visit. Patients were seen monthly for 9 months, or, for individuals who started hemodialysis or peritoneal dialysis, for 3 months thereafter.

RESULTS: 133 patients received FC and 66 received SOC. There were a higher proportion of diabetic patients in the SOC arm while other baseline characteristics were similar. 37% of patients in the SOC arm received P binders during the non-dialysis period. 30 patients assigned to FC(23%) and 31 patients assigned to SOC (47%) initiated HD/PD. Select baseline and on-study laboratory variables are shown in Table 1.

As compared to the SOC arm, treatment with FC resulted in statistically significant increases in mean TSAT, ferritin, and hemoglobin and statistically significant reductions in mean serum phosphate, and intact FGF23. Patients randomized to FC were significantly less likely to receive ESA or intravenous iron however after adjusting for baseline characteristics, reduction in ESA use was of borderline statistical significance (p = 0.06) while use of intravenous iron remained significantly reduced (p = 0.006).

Cumulative doses of ESA and IV iron were reduced in those receiving FC. The risk of RRT or death was significantly reduced with FC in the total cohort and among the diabetic sub-group (p = 0.0004 and p = 0.045 respectively). Figure 1. MMRM analysis demonstrated a modest but significant difference between change in the slope of eGFR between FC and SOC treatment arms (p = 0.049).

CONCLUSIONS: Administration of fixed dose ferric citrate to patients with advanced chronic kidney disease, regardless of entry serum phosphate, hemoglobin or iron sufficiency led to statistically significant increases in TSAT, ferritin, and hemoglobin, significant reductions in serum phosphate and intact FGF23, and reduced the exposure to ESA and intravenous iron prior to dialysis. There is a suggestion of benefit on time to death, dialysis or transplant for those assigned to FC even among the diabetic sub-group. These findings provide strong rationale for a larger, randomized, placebo-controlled trial of FC to optimize care in advanced CKD.
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DKK3 IN URINE IDENTIFIES PATIENTS WITH PROGRESSIVE CHRONIC KIDNEY DISEASE

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INTRODUCTION AND AIMS:
The number of patients with chronic kidney diseases (CKD) steadily increases, thereby, CKD represents a major socio-economic health burden. Accurate identification of patients who will suffer from CKD progression is challenging, but mandatory. The aim of the study was to explore the utility of urinary Dickkopf-3 (DKK3), a tubular-derived glycoprotein, as a biomarker for CKD progression.

METHODS:
To assess the prediction of CKD progression by urinary DKK3 in a prospective cohort study of patients with various CKD etiologies (N = 575) and annual follow-up (2,035 patient years), prospective clinical trial of patients with biopsy-proven IgA nephropathy (STOP-IgAN trial, N = 96) and cross-sectional general population study (N = 481).

RESULTS:
Median urinary DKK3/creatinine concentration was significantly higher in patients with CKD as compared to the general population (33 [126] vs. 431 [1,388] pg/mg; p < 0.0001). In kidney biopsy specimens (N = 76), higher urinary DKK3/creatinine levels indicated significantly higher tubulo-interstitial fibrosis, regardless of CKD etiology. In patients with CKD, urinary DKK3 concentrations were significantly associated with CKD progression. Urinary DKK3 > 1,000 pg/mg creatinine and > 4,000 pg/mg creatinine were associated with a mean annual eGFR decline of 2.4% (95% CI: -4.6 to -0.2%; p = 0.007) and 7.6% (95% CI: -10.9 to -4.2%; p < 0.001) independent of eGFR and albuminuria. Urinary DKK3 significantly improved prediction of loss of eGFR as compared to eGFR or albuminuria alone. In the STOP-IgAN trial, urinary DKK3 > 1,000 pg/mg creatinine was independently associated with a mean eGFR decline of 12.2% (95% CI: -16.9 to -7.4%; p < 0.003) during the six-month run-in-phase (N = 96).

In the following first six months of the treatment-phase (N = 57), a rise in urinary DKK3 concentration was associated with a significant (p = 0.001) eGFR decline, whereas stable or decreasing urinary DKK3 indicated a more favorable course of kidney function. This result was independent of the randomization to the intervention arms.

CONCLUSIONS:
Urinary DKK3 identifies CKD patients at risk for kidney disease progression, regardless of the cause of kidney injury. Therefore, urinary DKK3 might represent a novel diagnostic tool to improve the management of CKD patients and thereby to prevent the major burden of CKD.