Aims Sparsentan is a novel Dual Endothelin Angiotensin Receptor Antagonist (DEARA) being investigated for focal segmental glomerulosclerosis (FSGS) and IgA nephropathy (IgAN). It is a dual acting, highly selective antagonist of both the endothelin A receptor (ETAR) and the angiotensin II subtype 1 receptor (AT1R). The Phase 2 EPPIK study will examine the long-term antiproteinuric and nephroprotective potential and safety of sparsentan in pediatric patients with FSGS, minimal change disease (MCD), IgAN, IgA vasculitis (IgAV), and Alport syndrome (AS).

Methods The global, open-label, single-arm, multicenter study will evaluate the safety, efficacy, and pharmacokinetics (PK) of sparsentan in ~57 patients (aged ≥1 to <18 years), including ~30 with FSGS and/or MCD (population 1) and ~27 with IgAN, IgAV, or AS (population 2) over 108 weeks (figure 1). See table 1 for inclusion/exclusion criteria. Sparsentan will be administered in a novel liquid formulation at a dose adjusted to body weight.

Results Primary endpoints include safety (incidence of treatment-emergent adverse events) and efficacy (change in urine protein/creatinine ratio [UP/C] from baseline over 108 weeks) with sparsentan treatment. Secondary endpoints include PK outcomes, change from baseline over 108 weeks in albumin/creatinine ratio and estimated glomerular filtration rate (eGFR), and the proportion of patients with FSGS/MCD who achieve partial remission (defined as UP/C ≤1.5 g/g and >40% reduction in UP/C).

Conclusion This Phase 2 study will evaluate the long-term safety, antiproteinuric, and nephroprotective effects of sparsentan in pediatric patients with FSGS, MCD, IgAN, IgAV, and AS.
been associated with nephronophthisis (NPHP) and Jeune asphyxiating thoracic dystrophy, both of which are ciliopathies, but also with focal segmental glomerulosclerosis (FSGS), a glomerular kidney disease. During this search, there was a notable incidence (57%) of hypertension out of the 56 total cases, 84% of which aligned with a p.(Pro209Leu) variant. Searching the Genomics England 100,000 Genomes Project revealed one additional case of arterial hypertension associated with biallelic TTC21B variants.

Abstract 958

Abstract 958 Figure 1

Abstract 958 Table 1

| Patient Gender | Ethnicity | Age at referral | Clinical information |
|----------------|-----------|-----------------|---------------------|
| II.1 F         | British   | 3y, 6m          | Severe early-onset hypertension (99%), proteinuria, renal failure (3y, 7m), LV hypertrophy, liver function test abnormalities, growth retardation |
| II.2 M         | British   | 1y, 1m          | Severe early-onset hypertension (99%), renal failure (5y) |

Table 1: Clinical information for affected sibs solved for biallelic variants in TTC21B

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Abstract 1091 Table 1

| Parameter          | Grade I-II VUR (n, %) | Grade III-V VUR (n, %) | Chi Square | P
|--------------------|----------------------|------------------------|------------|---
| Stunting           | 3 (15.6%)            | 12 (54.5%)             | 24.36      | <0.001 |
| Thinning           | 8 (36.4%)            | 15 (63.6%)             | 7.68      | 0.0056 |
| Reversal UTI       | 12 (54.5%)           | 8 (36.4%)              | 0.14      | 0.7082 |
| Microalbuminuria   | 5 (13.6%)            | 5 (13.6%)              | 0.01      | 0.9176 |
| High serum cretine | 15 (63.6%)           | 15 (63.6%)             | 0.01      | 0.9176 |
| Sclerotin DMSA      | 12 (54.5%)           | 12 (54.5%)             | 0.01      | 0.9176 |
| Contracted kidney (renal volume >2×400 cm³) | 21 (95.5%) | 21 (95.5%) | 0.01 | 0.9176 |

Conclusion

In conclusion, biallelic variants in TTC21B have been shown to produce a wide spectrum of kidney phenotypes, resembling both NPHP and FSGS. This mixed tubulointerstitial and glomerular disease can often present with early-onset hypertension, and the diagnosis may be overlooked due to the lack of typical ciliopathy features. The addition of TTC21B to the early-onset hypertension gene panels can ensure a timelier genetic diagnosis for this rare tubuloglomerular kidney disease (figure 1).

Aims

To evaluate the long term renal outcome of children with Vesicoureteral reflux (VUR) and compare the outcome of Grade I-II VUR and Grade III-V VUR.

Methods

A total of 42 Patients with primary VUR (detected by Micturating Cystourethrogram) followed up for at least five years at the renal clinic, in a Teaching Hospital, Sri Lanka, were enrolled on the study. They were divided into two groups for the analysis: Grade I-II VUR and grade III-V VUR. Clinical data were extracted using clinic records. Anthropometric measurements, Blood pressure (BP), Urine for micro-albuminurea, Serum Creatinine were obtained at the time of study. Renal Ultrasound scan was done to measure the kidney size and to detect persistent VUR. Renal volume was calculated using Ellipsoid formula.1 2

Results

Among 42 children, 54.8% (n=23) were females, and 52.4% (n=22) had Grade III-V VUR (severe). The mean age of the Grade I-II VUR (mild) group was 95.40 (±30.6) months, whereas the other group had a mean age of 103.4 (±45.9). All children had at least one urinary tract infection, whereas 52.3% (n=22) had two or more episodes. Regarding the first UTI, the most prevalent organism was Escherichia coli (50%, n=21), whereas 9.5% (n=4) had atypical UTIs. In the severe VUR category, 13.6% (n=3) and 36.4% (n=8) children had stunting and thinness. However, the two groups showed no significant difference in stunting (p=0.3166) or thinness (p=0.1157). Higher grades of VUR had no predisposition to recurrent UTI (p=0.7683).

Microalbuminuria was observed in 22.7% (n=5) in the severe VUR group and 25% (n=5) in the mild VUR group. Among patients with higher VUR, 9% (n=2) had hypertension, and 13.6% (n=3) had elevated creatinine. No patient with mild VUR suffered from hypertension. More than half, 54.5% (n=12) patients with severe VUR had persistent ultrasonographic evidence of reflux, which was statistically significant compared (p=0.0022). Furthermore, renal scarring of at least one kidney was present in 63.6% (n=14) with severe VUR compared to 25% (n=5) in the mild VUR category (p=0.0276). However, the severe VUR group had 31.8% (n=7) at least one small/contracted kidney, whereas 25% (n=5) of children with mild VUR also showed small kidney (p=0.6251). Table 1 summarizes the results.

Conclusion

Higher grade VUR result in high chance of renal scarring. However, both higher grade and lower grade VUR can cause renal damage, microalbuminurea, and small contracted kidneys, hence need to follow up until adolescence or later life.

References

1. Batrum RJ, Smith EH, et al. The ultrasonic determination of renal transplant volume.J Clin Ultrasound.1974;2:281-285.