Methods: This is a retrospective study of the macroscopic nephrocalcinosis cases in adults treated in our department from January 1986 to October 2020

Results: 26 cases were diagnosed at a mean age of 35.28 years old with extremes ranging from 11 to 79 years old. The sex ratio M/F was 1. More than half of the patients had a family history of urolithiasis. Nephrocalcinosis was suspected following renal colic in 13 cases, a polyuric polydiabetic syndrome in 4 case, a hypokalaemia in 2 case, an urolithiasis in 2 case and a renal impairment in 2 case. In 3 case, the diagnosis was made fortuitly with an ultrasonography. The etiologies found were: familial distal tubular acidosis (6 cases), distal tubular acidosis caused by Sjögren’s syndrome (4 cases), primitive oxalosis (3 case), Cacci Ricci syndrome (3 cases), familial hypomagnesemia hypercalciuria (2 case), Dent syndrome (1 case) and no causes found (7 cases). Follow-up showed stabilization of renal function in 18 cases and the evolution into chronic kidney disease in 6 cases: 2 of them requiring renal replacement therapy after 5 years and the other died.

Conclusions: Nephrocalcinosis is prevalent both in children and adults. Its etiologies are numerous. Most of the metabolic disorders are genetic. The diagnosis of nephrocalcinosis requires a deep investigation with a global clinical assessment, laboratory tests and radiological evaluation. The final objective is to prevent ESKD.

No conflict of interest

POS-442

DISCOVERY OF CHK-336: A FIRST-IN-CLASS, LIVER-TARGETED, SMALL MOLECULE INHIBITOR OF LACTATE DEHYDROGENASE FOR THE TREATMENT OF PRIMARY HYPEROXALURIA

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Introduction: Primary hyperoxalurias (PH) 1-3 are a group of autosomal recessive disorders involving excess hepatic oxalate production and excretion. 

Methods: CHK-336 was evaluated in biochemical and cellular LDH activity assays across species and in vivo. CHK-336 was also performed.

Results: CHK-336 demonstrates potent and selective inhibition of LDH in human enzyme assays (IC50 = 0.4 nm) and in cryopreserved hepatocyte assays across species (IC50 = 80 – 131 nm). To minimize the potential for extra-hepatic LDH inhibition, a liver-targeted tissue distribution profile was engineered into the molecule. CHK-336 demonstrates exceptional liver-targeting across species at therapeutic doses (liver/plasma ratio, ~150 (rat, mouse) to >750 (cyno)) and active uptake into rat, cyno and human hepatocytes. Liver targeting is mediated by OATP-uptake into hepatocytes and tight binding to LDH results in a long liver half-life via target-mediated drug disposition that supports once-daily oral dosing. Furthermore, CHK-336 demonstrates a favourable off-target safety and ADME profile with minimal risk of important drug/drug interactions. In the PH1 mouse model, CHK-336 produced significant and dose-dependent reductions in urinary oxalate at low, once-daily oral doses to levels observed in wild-type mice. Wide safety margins were established in rodent toxicity studies to support continued development of CHK-336.

Conclusions: By potently blocking LDH, the terminal step in hepatic oxalate synthesis, along with the engineering of a liver-targeted tissue distribution profile, CHK-336 is a promising oral small molecule development candidate with the potential to treat patients with hyperoxaluria.


Conflict of Interest: Chinook Therapeutics

POS-443

AN UNUSUAL TREATMENT FOR 1,25 DIHYDROXY VITAMIN D3 - 24 HYDROXYLASE DEFICIENCY INDUCED HYPERCALCIURIA - CASE REPORT

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Introduction: Vitamin D metabolism plays a crucial role in calcium homeostasis. Not only does overproduction of 1,25(OH)2 Vitamin D3 lead to hypercalcaemia and hypercalciuria, but lack of degradation too. It is now well known that inactivating mutations in Vitamin D3 24 hydroxylase (CYP24A1) are associated with hypercalcemia, hypercalciuria and stone formation by reducing the degradation of 25(OH) and 1,25(HO) Vitamin D3. We here describe a patient in whom such mutations were associated with multiple calcium stones in the kidneys. A treatment with oral Hypericum perforatum (St-John’s Wort) to promote 1,25(OH)2 Vitamin D3 degradation through induction of CYP3A4 was proposed. This is the first case reporting the use of St-John’s Wort to treat hypercalciuria secondary to CYP24A1 deficiency.

Methods: Descriptive report of the patient clinical characteristics and history will be provided. Laboratory results including calcium levels, vitamin D and its metabolites levels, 24-hour urine collection before and after St-John’s Wort supplementation will be described.

Results: A 35-year-old Caucasian male known for familial hypercalciuria was evaluated for a history of renal stone formation that had begun more than 10 years previously. Laboratory tests revealed mild hypercalcemia and hypercalciuria, 25(OH) and 1,25(OH)2 Vitamin D3 serum levels of phosphorus, 25(OH) Vitamin D3 and 1,25(OH)2 Vitamin D3 and very low or undetectable serum levels of PTH, PTHrP and 24,25(OH)2 Vitamin D3 serum levels. Genetic testing also revealed a homozygous pathogenic mutation in CYP24A1 (NM_000782.4: c.400T>G; p.Trp134Gly) as the cause of hypercalciuria in this case. While the patient refused to be treated with ketoconazole, an 1-alpha hydroxylase inhibitor, he accepted to try the St-John’s Wort extract (300 mg tid), a CYP3A4 inducer that is also involved in 25(OH) Vitamin D3 and 1,25(OH)2 vitamin D3 degradation (Fig. 1). To our surprise, this treatment led calcium to decrease from 9.1 to 3.6 mmol/day after a few weeks.

Conclusions: To our knowledge, this is the first report of the use of St-John’s Wort supplementation to reduce calcium in a patient genetically inactivated for CYP24A1. This observation could pave the way towards the use of St-John’s Wort in the treatment of hypercalciuric renal stone disease of different causes in other patients. Moreover, this therapeutic option does not bear the severe adverse effects of other therapy, namely: androgen induced by ketoconazole and positive calcium balance with thiazide diuretics.

No conflict of interest

POS-444

ACUTE FOCAL BACTERIAL NEPHRITIS IN ADULTS: A SINGLE CENTER EXPERIENCE

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Introduction: Acute Focal Bacterial Nephritis (AFBN) resembles clinically acute pyelonephritis (APN) and remains an underdiagnosed condition. Therefore, the condition is managed as APN and the renal lesions insufficiently treated may progress to abscess leading to necrotomy. Contrast-enhanced computer tomography (CECT) makes the diagnosis by showing wedge-shaped parenchymal areas with decreased enhancement. However CECT is not regularly requested. We report here our experience with the management of 17 consecutive cases admitted with AFBN and look at the clinical features that may help differentiating AFBN from APN.

Methods: We looked at the data of all patients diagnosed as AFBN and admitted from January 2017 to May 2020. The medical team dealing with AFBN was all aware of the importance of getting biological and clinical findings accurately in order to find out differences between APN and AFBN, and the importance of requesting a CECT (even if kidney ultrasound was available and highly suggestive). All cases of AFBN were managed by the same medical staff and the protocol adopted is to treat with antibiotics for at least 3 weeks followed by a repeated CECT.

Results: All patients were females, admitted with high grade fever, flank pain and uncomfortable general condition. The mean age was 23 years. Among the classical symptoms we could notice that fever and flank pain were persisting for at least 3 days. Nausea and vomiting were regularly present for the first 2 days. Dysuria was present in 2 patients only. Among the non-classical symptoms, we noticed a headache in 10 patients (among which 2 patients had severe headache), which resolved gradually after starting antibiotics and acute kidney injury in one patient with gradual recovery of kidney function. Kidney ultrasound and Doppler done in all patients suggested the diagnosis of AFBN in 9 patients. CECT done in all patients confirmed the diagnosis. The 3-weeks length of antibiotic treatment was sufficient for the majority of the patients with complete resolution of the CECT findings and only 3 patients required an additional week of antibiotics.

Conclusions: Besides persisting high grade fever and flank pain, we noticed also a high prevalence of headache in our patients diagnosed with AFBN. Headache was also reported in some cases in the literature. We may therefore recommend it as a potential high alert symptom in favor of AFBN, triggering a request for CECT.

No conflict of interest

POS-445
ACUTE PYELONEPHRITIS IN CHILDREN WITH CONGENITAL ANOMALIES OF KIDNEY AND URINARY TRACT (CAKUT): ABOUT A SERIES OF 45 CASES

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Introduction: Acute pyelonephritis (APN) is the most common complication of CAKUT in children. Their recurrence leads to antibiotic resistance, as well as to kidney scarring which can result in chronic kidney disease. Hence, the importance of early diagnosis and appropriate management.

Methods: In this study, we try to define the most frequent symptoms and infectious agents associated with APN in children with CAKUT. For that, we gathered retrospective data of 45 patients, aged below 15-year-old, with a medical history of CAKUT and presenting to our hospital for APN. This study was conducted from January 2015 to June 2020.

Results: The median age at diagnosis was 3±2 years, with half of the patients aged below one-year-old. The majority of our patients were boys (sex ratio of 2.8). Recurrent pyelonephritis was reported in 87% of cases, with a median of five episodes per child.

Extra-urinary symptoms were frequently observed in our children, mostly acute fever, gastro-intestinal signs (diarrhea, vomiting, abdominal pain). Low back pain, urinary flow abnormalities, signs of bladder irritation were very rare. Physical examination was generally poor.

Laboratory tests found high CRP levels, leukocytosis, and high granulocytes count in all patients.

E-Coli was responsible for APN in one-third of cases, followed by Klebsiella in 24%, and Enterobacter in 7% of cases.

The proportion of different CAKUT types was as follows: posterior urethral valve in 40%, reflux in 21%, megaureter in 18%, pyelo-ureteral junction syndrome in 8%, and ureterocele in 5%.

Two or more than two CAKUT were associated with 26% of our children.

The majority (73%) of our children were under antibiotic prophylaxis using trimethoprim-sulfamethoxazole.

Antibiotic resistance was very common in our patients, with 30% amoxicillin-clavulanic acid resistance and 15% third-generation cephalosporin resistance. Quinolones and imipenem were the least used antibiotics for the management of APN in our patients, and this explains the lowest share of resistance with 1.5% and 0.7% respectively.

Management of APN was based on prescribing an association of two synergic antibiotics, and it was the third-generation cephalosporin + aminoglycoside in most cases (67%).

Three-quarters of our patients had surgical interventions to correct the CAKUT.

As for renal prognosis, three of our children developed chronic kidney disease in the long term, of whom one had to undergo hemodialysis for end stage kidney disease.

Conclusions: Recurrent APN is still a challenging problem in children with CAKUT. Surgical management of CAKUT can lower the frequency of infection and improve renal prognosis. Hence the importance of early diagnosis of CAKUT, especially in the antenatal period.

No conflict of interest