REPAIR

(Inflammation REduction to Prevent cArdiovascular Injury in Renal disease Trial)

Background

Cardiovascular disease common in people with CKD
- Risk associated with inflammatory markers in general
- Patients with CKD, especially kidney failure, commonly have elevated inflammatory markers

Colchicine
- anti-inflammatory
- promise in reducing cardiovascular events
- May improve kidney function

Colchicine in CKD patients controversial
- Renally cleared
- Tolerability linked to dose

Rationale

Determine whether either of 2 low doses of colchicine tolerated in patients with advanced kidney disease.
Informs current use for gout and pericarditis
Informs future trials

Objectives

Primary Objective:
To determine among adults with severe chronic kidney disease not requiring dialysis and (separately) in those requiring dialysis, the proportion who, over 8 weeks of treatment, discontinue colchicine 1) 0.3 mg daily and 2) 0.6 mg daily.

Secondary Objective:
To determine the reasons for temporary and permanent discontinuations of colchicine at the 0.3 mg and 0.6 mg daily doses.
To determine degree of adherence to colchicine at the 0.3 mg and 0.6 mg daily doses.
To determine the risk of major side effects of colchicine at the 0.3 mg and 0.6 mg daily doses.

Tertiary Objectives:
To determine changes in hematologic markers, inflammatory markers, muscle damage, and hepatocellular injury; proteinuria (REPAIR CKD only), and the serum concentrations of colchicine achieved at the study doses, as well as to determine sex differences in permanent discontinuation of the study drug.

Eligibility Criteria- Inclusion

Inclusion requires all the following are present:

1.One of either:

I.Estimated GFR using CKD-EPI 2021 equation of ≤30 ml/min/1.73m2 on at least two occasions separated by at least 2 months and do not yet require dialysis and are not expected by their treating nephrologist to require dialysis in the next 6 months (**REPAIR CKD cohort**), or

II.receiving chronic maintenance dialysis 2 or more times per week for the previous 90 days (**REPAIR Dialysis cohort**);

2.Age ≥18 years

3.Provide informed consent to participate.

Eligibility Criteria- Exclusion

Exclusion is required if any of the following are present:

1. Currently treated with and cannot withdraw colchicine due to medical necessity; or
2. Known allergy/sensitivity to colchicine; or
3. Prior self-reported intolerance to colchicine at a dose of 0.6 mg daily or lower; or
4. Currently pregnant or planning to become pregnant or breastfeed during the study; or
5. Of childbearing potential AND do not have a negative pregnancy test OR do not agree to use two forms of contraception for the duration of the study; or
6. Anticipated living donor renal transplant within the next 6 months; or
7. Using a strong inhibitor of p-glycoprotein or strong inhibitor of CYP3A4 in the last 14 days;
8. B12 deficiency not managed with intramuscular supplementation; or
9. Uncontrolled chronic diarrhea; or
10. Cirrhosis, or chronic active hepatitis; or
11. Pre-existent neuromuscular disease or persistent serum CK level > 3 times the upper limit of normal as measured within the past 60 days and determined to be non-transient through repeat testing; or
12. Patient with any of the following as measured within the past 60 days, and determined to be non-transient through repeat testing:
    - white blood cell count < 3.0 X 109/L; or
    - platelet count <110 X 109/L; or
    - ALT or AST > 3 times the ULN; or
    - total bilirubin > 2 times ULN and not due to Gilbert syndrome
13. Patient is considered by the investigator, for any reason, to be an unsuitable candidate for the study.

Study Flow Diagram

- Phase 2 basket trial including 2 open-label single-arm cohorts: REPAIR CKD cohort and REPAIR Dialysis cohort
- Open label colchicine 0.3 mg daily for 8 weeks followed, in patients who tolerated the 0.3 mg dose, by forced titration to 0.6 mg daily for 8 weeks.
- Sample Size: ~200 pts
  - REPAIR CKD cohort 100 pts
  - REPAIR Dialysis cohort 100 pts