Global Action. Local Change.

KDIGO Controversies Conference on Nephropathic Cystinosis

December 11-13, 2014
Lisbon, Portugal

Kidney Disease: Improving Global Outcomes (KDIGO) is an international organization whose mission is to improve the care and outcomes of kidney disease patients worldwide by promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines. Periodically, KDIGO hosts conferences on topics of importance to patients with kidney disease. These conferences are designed to review the state of the art on a focused subject and to ask conference participants what needs to be done in this area to improve patient care and outcomes. Sometimes the recommendations from these conferences lead to KDIGO guideline efforts and other times they highlight areas for which additional research is needed to produce evidence that might lead to guidelines in the future.

Background

Nephropathic Cystinosis (OMIM #219800) has been known for well over a hundred years but not until the end of the last century was its molecular defect discovered. Mutations in cystinosin (CTNS, 17p13.2) that prohibit egress of cystine from within lysosomes is an underlying genetic defect in all patients, and when untreated, leads to terminal kidney failure and disruptions in most other organ functions including eyes, the brain, endocrine glands, muscles, bone, heart, and linear growth. Well over 100 mutations in cystinosis have been described. There is limited genotype-phenotype

correlation of disease severity in juveniles and adults but much less so for the infantile form.

The exact mechanisms whereby disruption of cystinosin leads to such devastating systemic consequences in nephropathic cystinosis are uncertain. *In vitro* and *in vivo* studies suggest multiple pathways leading to clinical disease, including impaired vesicle trafficking, enhanced apoptosis, cell dedifferentiation, and a reduced capacity to deal with oxidative stress and inflammation.

At present, therapy in nephropathic cystinosis is directed to the reduction of intracellular cystine (as measured by [white blood cell [cystine]/ mg cell protein]) in an effort to forestall the onset of chronic kidney disease and other organ dysfunctions. The use of such cystine depleting therapy has been challenging due to the need to take cysteamine (β-mercaptoethylamine), often formulated as a bitartrate salt, for every six hours around the clock. Recent introduction of a delayed release form of cysteamine bitartrate has been promising since it has been shown to be effective when used every 12 hours in clinical trials that have been conducted for more than two years to date.

It is hoped that a deeper understanding of the cell biology of nephropathic cystinosis will likely provide significant insight into the pathogenesis of tubulointerstitial fibrosis and glomerular dropout, a hallmark of virtually all types of kidney disease including nephropathic cystinosis, and perhaps identify new therapeutic strategies. To this end, the animal model of the disease has been rescued by innovative bone marrow and stem cell transplantation strategies and human trials are planned quite soon.

Longer survival of children with cystinosis due to advances of cysteamine therapy and the availability of kidney transplantation transformed cystinosis from a lethal pediatric disease into a disorder with which patients can now reliably reach adult age. Prolonged life expectancy has revealed several new challenges in adult patients mainly caused by extra-renal disease symptoms such as severe myopathy, neurological problems, and male infertility. Transition from pediatric to adult clinics is now a critical exercise because the disease is largely unknown among physicians involved in adult renal care.

Conference Overview

The objective of this KDIGO conference is to gather a global panel of clinical and scientific experts who will address key issues related to the cell and molecular biologic consequences of cystinosin deficiency, establish the optimal diagnostic workup to arrive at the diagnosis of nephropathic cystinosis early in life or recognize its later-age presentations, and discuss the unique aspects of management and treatment in the child, adolescent, and adult years. It is hoped that assessing our current state of knowledge will not only improve the characterization of nephropathic cystinosis but will also facilitate communication between researchers and inform clinicians of the evidence base for present treatment options. This conference will also put forth a summary of the outstanding knowledge gaps and propose a research agenda.

Drs. Craig B Langman (Feinberg School of Medicine, Northwestern University, Lurie Children's Hospital of Chicago, Chicago IL, USA) and Elena Levtchenko (University Hospitals Leuven & Katholieke Universiteit Leuven, Belgium) will co-chair this conference. The format of the conference will involve topical plenary session

presentations followed by focused discussions on key clinical issues as outlined in the **Appendix: Scope of Coverage**. The conference output will include publication of a position statement that will help guide KDIGO and others on therapeutic management and future research.

APPENDIX: SCOPE OF COVERAGE

1. **Basic and translational science**

    - How does cystine exit from cystinotic lysosomes to interact with cell metabolism, and how are the pathological effects of lysosomal cystine storage mediated?

    - Apoptosis is increased in cystinotic tissue and the increase is linked to lysosomal cystine storage. Mediators include PKC ∂, AMP Kinase and Caspase 4. Are there other mediators and/or modulators of this process?

    - The primary question that must be addressed is how does isolated lysosomal cystine interact with the 10mM GSH in the cytosol to yield an abnormal redox state? The existent data on abnormal redox potential in cystinotic cells give conflicting results. Are these the result of differing systems and assays? How does stored cystine affect the cytosolic redox state?

    - Do cystine crystals promote chronic renal interstitial fibrosis? Could improvement after bone morrow transplantation be secondary to the replacement of renal cystinotic histiocytes with wild-type cells?

    - Do other functions of cystinosin that are not related to cystine lysosomal transport explain the Fanconi syndrome and its unresponsiveness to cysteamine?

    - Does bone morrow transplantation represent a valid treatment option in humans? What are the mechanisms that mediate the observed effects in animals? Will these same mechanisms work in humans? Should the approach involve gene therapy or the use of HLA identical bone morrow?

2. Diagnostics and biochemical follow-up

- Is it feasible to perform pre-symptomatic screening of cystinosis? *In utero* and in newborns?
- What is the optimal technique for white blood cell (WBC) isolation and storage?
- What is the optimal technique for WBC cystine measurement, including timing of the measurement?
- Are there alternatives to WBC cystine measurements to monitor cysteamine treatment (plasma cysteamine, others)?
- What is the role of cystine as a biomarker and cysteamine blood levels as a surrogate?
- Can we measure crystal loads?
- Is genetic diagnosis mandatory?
- Is urine analysis helpful to raise the suspicion or make the diagnosis?
- What other biochemical monitoring should be undertaken in treated patients?
- What are the major clinical hints, providing high index of suspicion to diagnose cystinosis as early as possible?
- What is the final decision regarding carnitine supplementation for patients post transplant? Is therapy worth the cardiovascular risk?

3. Management of infants and children with cystinosis

- How to manage challenging nutritional issues in cystinosis?
  - Tube feeding
  - Vomiting
  - Caloric recommendations
  - Carnitine
  - Copper, zinc status
  - Vitamins

- Management of polyuria
  - Indomethacin
  - Bladder function
  - Monitoring urine volume

- When/how to use growth hormone?

- Management of electrolyte losses in Fanconi Syndrome
  - Salt supplementation
  - Calcium and phosphate homeostasis
  - Hypokalemia
  - Acidosis

- When and how to introduce cysteamine therapy?
  - Timing
  - Dose
  - Monitoring
  - PPI
  - Slow release cysteamine

- Management of eye disease
  - Eyedrops/side effects
  - Compliance
  - Long acting formulation

- Management of thyroid disease
  - Is there a critical TSH level to commence replacement?

- Management of early neurologic manifestations
  - Learning disorders
  - Raised ICP

- Management of progressive renal failure
  - ACE inhibitors for proteinuria
  - LRD transplantation and heterozygous donor (parent) issue
  - Pre-transplant nephrectomy

- Any required measures to enhance care for cystinosis in developing nations given the existing gap as compared to developed nations?

4. **Adolescent issues**
    - How to manage halitosis?
    - Is the bone disease of cystinosis in infancy replaced by another?
    - How should social adaptation of cystinosis patients be supported?
    - Can cystinosis patients perform all jobs? Is there an effect of neural disease on job training and performance?
    - Is there a special adaptation of therapeutic education and psychological back-up to adolescents
    - Is there a preference for a particular form of RRT in cystinosis patients?
    - Should cysteamine dose be adapted in patients on RRT? Optimal dose recommendations?
    - How should the onset of the need for a kidney transplant impact substrate reduction therapy?
    - Do cystinosis patients need a special preparation to renal transplantation?
    - Do cystinosis patients need different immunosuppressive therapy after renal transplantation?
    - How should cystinosis patients be prepared for the transition to internal medicine clinics?
    - How should pediatrician and adult teams be prepared for the transition to internal medicine clinics?
    - How should the recognition of systemic disease impact the therapeutic approach?

5. **Adult patient issues and the management of extra-renal manifestations of cystinosis**
    - What is the chronology of organ dysfunctions in adults with cystinosis and which are amenable to substrate depletion therapy?
    - What is the impact of early treatment with cysteamine on the onset of extra-renal complications?
    - What is the optimal cysteamine dose in adult cystinosis patients?
    - Is there evidence for life-time therapy with substrate-depleting agents?

- What are the adherence issues for cysteamine treatment?
- How to address the issues of family planning and male fertility?
- How to manage neurological complications of cystinosis?
- How to manage cystinosis myopathy, including growth hormone?
- What is the optimal multi-disciplinary follow-up of cystinosis patients?
- Who are the relevant physicians-specialists to participate in cystinosis clinics?
- Which are the specificities of late-onset form of cystinosis?

Overall for Conference Chairs to address: What is the role of a global registry in advancing clinical trials/research for cystinosis?