Global Action. Local Change.

KDIGO Controversies Conference on

Diagnosis and Management of Patients with Fabry Nephropathy

October 16-18, 2015

Dublin, Ireland

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

Fabry disease is an X-linked lysosomal storage disorder caused by deficient activity of alpha-galactosidase A.[1-2] This results in the pathologic accumulation of multiple substrates, particularly globotriaosylceramide (GL-3, Gb3, CTH) in the vascular cell (endothelium, smooth muscle cells, pericytes), the mesangium- most prominently in podocytes, interstitial and tubular cells, and in other cell types in the heart and the brain (mostly in the vasculature).[3-5]

Initially the disease was exclusively described in men but women are substantially affected as well, although this may be in later stages of life and to a variable degree.[6] The prevalence of Fabry disease around the world is approximately one in 40,000 individuals which therefore can be classified as a rare inherited disease.[7] In parallel to the advent of replacement therapy for the deficient enzyme alpha-galactosidase, there has been an increase in our understanding of the pathogenesis, clinical presentation and approach to the management of Fabry disease but our knowledge remains incomplete. Expert opinions about specific treatment with enzyme placement therapy have been written[8-10] and long-term results of treatment efficacy were published recently.[11-15] There is still ongoing controversy concerning the role of early screening and diagnosis of Fabry disease with respect to certain genetic mutations as well as issues on biomarkers, efficacy, dosing, and timing of treatment.[10,13,16-18] While we are still awaiting results of randomized trial in children,[19] new approaches to the treatment of Fabry disease are appearing on the horizon.[20]

Relevance of the topic and the conference

There is a strong public health and economic imperative to improve outcomes for people with Fabry disease overall, particularly those with kidney disease. Although enzyme replacement therapy may slow the progression of some aspects of the disease, further advances have not been forthcoming. The relative effectiveness of enzyme treatment in specific groups of patients is unclear and the role of antibody formation is not well understood. The efficacy and role of adjunctive treatments such as renin-angiotensin system blockade, vitamin D supplementation, anti-platelet agents, cholesterol and blood pressure-lowering strategies as well as device support (e.g.,

pacemaker, implantable cardioverter defibrillators) in ameliorating progressive organ damage will be further addressed and discussed at this conference.

Conference Overview

Management of Fabry disease should not only be limited to the kidney but should also take into account the multisystemic nature of the condition. Proper management should occur at the direction of a comprehensive, longitudinal, multidisciplinary care team that incorporates the expertise of multiple Fabry disease specialists to assist in the management of organ-specific complications and recommend the use of available therapies where appropriate. To this end, this KDIGO conference will gather a global panel of multidisciplinary clinical and scientific expertise (e.g., nephrologists, cardiologists, neurologists, geneticists, pediatricians) that will identify key issues relevant to the optimal managementand treatment of Fabry disease. The objective of this conference is to assess our current state of knowledge related to cell and organ damage by Fabry specific and unspecific mechanisms and its treatment; approaches to screening and diagnosis as well as biochemical and histological follow-up of Fabry disease; optimal prevention of kidney disease; and management for the reduction of comorbidities such as extrarenal organ involvement. The overarching goal is to summarize the current knowledge gaps and propose a research agenda to resolve standing controversial issues. It is hoped that this conference will inform clinicians of the evidence base for present treatment options and help pave the way for future studies in this area. We anticipate deliberations from this Controversies Conference will also identify patient-centric issues (e.g., genetic testing, specialist referral, quality of life, optimal Models of Care, etc.) to further inform the agenda of our upcoming

summation conference addressing common challenges faced by patients with rare kidney diseases.

Drs. Christoph Wanner (University of Würzburg Hospital, Germany) and Raphael Schiffmann (Baylor Research Institute, Dallas, Texas, USA) will co-chair this conference. The format of the conference will involve topical plenary session presentations followed by focused discussion groups that will report back to the full participant group for consensus building. Invited participants and speakers will include worldwide leading experts who will address key clinical issues outlined in the **Appendix: Scope of Coverage** (page 7). The conference output will include publication of a position statement that will help guide KDIGO and others on therapeutic management and future research on Fabry disease.

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Appendix: Scope of Coverage

Topic Group 1: Screening & Diagnosis

A: Screening strategies

Q1: Should Fabry disease be screened systematically at any age and if so in what populations?

Q2: Should Fabry disease be screened for in the newborn period?

Q3: What is the best screening strategy for early diagnosis of Fabry disease? (e.g., newborn screening, high-risk screening of symptomatic patients, cascade screening of family members)

Q4: What is the impact of positive genetic diagnosis on asymptomatic patients and how can this be mitigated?

Q5: What techniques should be used in any of the above screenings?

Q6: What signs and symptoms should trigger screening for Fabry disease in individuals without a family history of Fabry disease? What is the importance of drug-induced phenocopies?

Q7: Are there any clinical manifestations which are pathognomonic of Fabry disease?

Q8: At what age should we screen for Fabry disease in symptomatic patients?

Q9: At what age should we screen for Fabry disease in asymptomatic family members? Should all family members be screened according to pedigree analysis or should symptom triggers be used? If so, which symptoms?

Q10: What is the role of genetic counselling and prenatal diagnosis?

B: Establishing disease status

Q11: What are the recommended assessments at different ages for monitoring kidney involvement in Fabry disease? At what intervals should assessments be repeated?

Q12: Which Fabry patients should have a kidney biopsy or a follow-up biopsy?

Q13: What are the indications for kidney biopsy in a known Fabry patient?

Topic Group 2: Enzyme Replacement Therapy (ERT)

Q1: Is current ERT effective in Fabry disease and if so for what aspects of the disease?

Q2: When to treat (and when not to treat). Do we know when to initiate ERT (e.g., age, sex, presence/absence of clinical manifestations, non-classical disease patients)?

Subquestions within **Q2**:

- Which patients should be treated? Which patients should not be treated?
- What is the role of the GLA variant, or the residual alpha-galactosidase A activity, regarding initiation of therapy?
- When should ERT be discontinued (how is treatment failure defined)?

Q3: How to monitor therapy. What criteria can be used to determine the effectiveness of ERT and how can ERT best be monitored?

Subquestions within **Q3**: (For each criterion, explain adequate timeframe)

- Should renal globotriaosylceramide burden serve as the primary outcome measure?
- Is there a role for "trials" of ERT for a limited time period in advanced disease?
- What is the role of biomarkers (plasma (lyso)Gb3 or urinary (lysoGb3))?

Q4: What is the evidence for dose response of ERT?

Subquestions within **Q4**:

- What is the role of the GLA variant, or the residual alpha-galactosidase A activity on choice of therapy?
- What is the role of neutralizing antibodies on effectiveness of ERT and choice of therapy?

Q5: Is there a role for expert centers in the diagnosis and treatment of disease burden and ERT prescription? Would this be different in low- and middle-income countries (LMICs)?

Q6: Are there clinically relevant drug interactions with ERT (e.g., amiodarone)?

Topic Group 3: Non-specific standard of care therapy

Q1: What types of Fabry-specific adjunctive treatments are most likely effective?

Q2: Can a kidney care strategy be recommended for LMICs including standard of care for preventing progression?

Q3: What are the criteria for introducing renin-angiotensin-aldosterone system (RAAS) inhibitors?

Q4: What is the endpoint for RAAS inhibitors treatment and other anti-proteinuric therapies in Fabry disease?

Q5: What are the optimal antiplatelet agents for use in Fabry disease?

Q6: Should there be primary prevention for stroke in Fabry disease?

Q7: What is the optimal treatment for neuropathic pain?

Q8: Should patient-reported outcome measures (PROMs) or even patient-reported experience measures (PREMs) be routinely collected in Fabry registries, and if so which ones?

Q9: Is there a role for a trial that investigates effectiveness of ERT versus optimal standard of care in attenuated phenotypes?