Global Action. Local Change.

KDIGO Controversies Conference on Glomerular Diseases

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Singapore

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

Glomerular diseases, excluding diabetic nephropathy, account for about 25% of the cases of chronic kidney disease worldwide.[1, 2] However this varies considerably between countries from a low of about 10% in Latin America to over 50% in China.[1] In the United States, the prevalence of end-stage kidney disease (ESKD) due to a glomerular disease is about 300 per million population, making glomerular disease the third most important cause of ESKD in the country.[3] Given the magnitude of long-term morbidity from glomerular diseases and in particular its frequent manifestation in younger patients, it is critical that they be diagnosed efficiently and that management be optimized to control disease and prevent progressive renal insufficiency.

Traditionally the diagnosis of a glomerular disease rests on the histologic evaluation of a kidney biopsy. The kidney biopsy or the ability to interpret the biopsy is not

universally available throughout the world and even when available, some platforms, such as electron microscopy may not be readily accessible. Therefore an unmet need in the nephrology community is the identification of serum or urine biomarkers of renal pathology to supplement, or in some cases substitute for the biopsy, at least in developing nations. For some glomerular diseases, like membranous nephropathy, anti-phospholipase A2 receptor antibody titers begin to address this need but how to use this antibody to optimize clinical management is still controversial.[4] Biomarkers of kidney histology are being sought in other glomerular diseases.[5]

In nations with more access to health care resources, the question arises whether simple histology of the kidney is sufficient to evaluate the kidney biopsy, or if the application of molecular pathology may add to our understanding of disease heterogeneity within types of glomerular disease that could be used to optimize treatment.[6, 7]

The management of glomerular disease depends on the type of glomerulonephritis (GN), but in almost all cases relies on non-specific, broad-spectrum immunosuppression. This results in suboptimal efficacy and considerable drug-related toxicity.[8] A number of randomized clinical trials of novel immunomodulatory therapeutics have been conducted over the last few years in several glomerular diseases. Overall many of these trials have not succeeded, but important lessons may be taken from these failures. On the other hand, a few novel drugs have been approved and a few phase II trials have been very promising.[9] This increasing menu of available drugs adds to the confusion of how to treat patients and raises the question of sorting out newer drugs from both the successful and failed trials.[9-14]

The effects of therapy in glomerular diseases are followed clinically by changes in proteinuria and kidney function (serum creatinine concentration [SCr] or estimated glomerular filtration rate [eGFR]). Proteinuria has not been accepted by the US Food and Drug Administration as a sufficient endpoint for clinical trials in general, but there now seems to be a change in this position, especially if specific levels of proteinuria can predict specific long-term kidney outcomes for individual GNs.[15, 16]

Proteinuria is a reasonable marker early in disease, but over time, and with scarring of the renal parenchyma, it becomes difficult to distinguish proteinuria due to disease activity from proteinuria due to obliterative nephropathy from nephron loss. In addition, SCr and eGFR are also poor markers of intact nephron mass. Thus the best ways to follow patients with glomerular disease have not been established. This is an area waiting for biomarkers to be identified and validated, but until that time guidelines on the interpretation and application of traditional clinical parameters must be reviewed.[17]

Conference Overview

The objective of this KDIGO conference is to gather a global panel of multidisciplinary clinical and scientific expertise (i.e., nephrology, pathology, rheumatology, pediatrics, etc.) to identify key issues relevant to the optimal management of primary and secondary glomerular diseases. The goal of this KDIGO conference is to determine best practice treatment and areas of uncertainties in the treatment of glomerular diseases, review key relevant literature published since the 2012 KDIGO GN Guideline, identify topics or issues that warrant revisiting for future guideline updating, and outline research recommendations needed to improve GN management.

Drs. Jürgen Floege (University of Aachen, Germany) and Brad Rovin (Ohio State University, 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 group for consensus building. Invited participants and speakers include worldwide leading experts who will address clinical issues as outlined in the **Appendix: Scope of Coverage** below. The conference output will include publication of a position statement to help guide KDIGO and others on therapeutic management and future research in glomerular diseases.

Appendix: Scope of Coverage

Group 1: General Principles, Membranoproliferative GN (MPGN), C3 Glomerulonephritis (C3GN)

1. **General principles (I)**

- What constitutes the optimal target blood pressure, lipid levels, fluid and dietary sodium intake in glomerular disease? Is there a best way to choose the type of RAS blockade (ACE inhibitor or ARB, or in combination), diuretics and their dosage in patients with glomerular disease? How are these drugs best adjusted in the presence of nephrotic syndrome and/or progressive decline in GFR? Is there an order that is preferable in terms of the introduction of antihypertensive agents beyond RAS blockade and diuretics?

- Are there specific indications where RAAS blockade should not be considered for glomerular disease? Role of an apparent fall in GFR after RAAS blockade: good or bad (correcting hyperfiltration vs. AKI)? When and how should we introduce the "sick day "concept to withholding RAS blockade? Should there be a low GFR cut-off for discontinuing RAAS blockade? Should RAAS blockade be started and up-titrated in patients who have or develop hypotension during treatment? In patients with persistent high-grade proteinuria, should RAAS blockers be increased above the maximum daily dose that is recommended for hypertension? Is there any evidence that RAAS blockade may reduce proteinuria but mask ongoing inflammation in glomerular diseases when immunosuppression is contemplated or being used? (discussions on RAAS blockade should include agents such as direct renin inhibitors, mineralocorticoid blockers, and epithelial sodium channel blockade)

- What other lifestyle modifications (e.g., diet, exercise, sleep health, tobacco use) are generally advisable? What is the potential mechanism by which obesity contributes to CKD and in particular glomerular disease pathogenesis and progression? What medications should be considered (e.g., vitamin D,

statins and SGLT inhibitors) beyond RAS blockers? What should be avoided (e.g., non-dihydropyridine calcium channel blockers)?

- What are clinically relevant endpoints for glomerular diseases? (should address/comment on biomarkers in general including markers of tubular damage)
  What are the important aspects of study design in glomerular disease with respect to the regulatory approval decision-making process? Which method of monitoring proteinuria should be used in therapeutic decision making in clinical practice?
  Should hematuria be used as a marker of disease activity and/or a surrogate endpoint? If so in which specific diseases should it be measured and how (i.e., morphology examination; semiquantitative vs. quantitative)?

- What is the evidence that there is a contribution of birth weight and/or nephron mass to the pathogenesis and progression of glomerular disease?

- Is there a standard approach which could or should be applied to both developed and developing countries despite resource limitations in the diagnosis and treatment of glomerular disease?

2. **Nephrotic syndrome**

- Is there a time to introduce prophylactic anticoagulant therapy and if so for how long, and which drugs should be used? (dose adjustment necessary by GFR?) Does the approach in membranous nephropathy (MN) differ from other glomerular diseases associated with the nephrotic syndrome?

- What is the optimal approach to treating hyperlipidemia? What should be the goal? What are the recommendations of the use of prophylaxis (e.g., for infections, gastrointestinal bleeding, osteoporosis) in patients being treated with immunosuppression? What are the recommendations in regards to the timing and type of vaccinations in patients with glomerular disease?

3. **MPGN (i):** Explain that MPGN is a pattern of injury rather than a disease entity. Is the division in the histologic classification of MPGN into immune complex-mediated and complement-mediated GN sufficient? What is the likelihood of overlap and is this dependent on timing (trajectory) or presumed etiological type? If so, what should be the sequence and limit of diagnostic investigation in clinical practice? Are there are specific monitoring tools and if so, in which specific variants? In which cases should pronase immunofluorescence of kidney biopsy tissue be performed?

4. **MPGN (ii):** How should paraprotein-associated MPGN ("monoclonal gammopathy of renal significance") be evaluated? What is the approach to therapy based on this workup? What are meaningful clinical endpoints in this disease?

5. **MPGN (iii):** What is the appropriate workup for other variants of MPGN, particular in so-called idiopathic MPGN, and should other types of deposition disease such as fibrillary and immunotactoid GN be included? Which of these variants require immunosuppressive therapy, and what should be used as clinically meaningful endpoints for treatment (e.g., proteinuria/change in GFR)? What is the evidence to support immunosuppressive therapy here? What is the approach to the diagnosis, treatment and monitoring of hepatitis C-associated glomerulonephritis?

6. **MPGN (iv):** In complement associated/mediated MPGN, how specifically can dysregulation of the different complement pathways (classic, lectin, alternate) be demonstrated, and can this inform the use and development of complement inhibitors for these diseases? What is the role of eculizumab in C3G? Where are we in the development of additional complement inhibitors today? Where do they act in the complement cascade and is there likely to be specificity of these drugs in relationship to specific complement associated/MPGN variants? What is the distinction in C3 dominant infection-associated GN? Are there special considerations in the pre- and post-transplant management of patients with ESKD due to MPGN/C3 glomerulopathy?

Group 2: IgA Nephropathy (IgAN)

Pathogenesis

1. Are there new insights into pathogenesis that can guide treatment?

Biomarkers & prediction of prognosis

2. Which clinical, laboratory and pathologic parameters should form the basis for risk assessment? Should microhematuria (qualitative or quantitative?) be incorporated in the risk assessment?

3. What is the role of new biomarkers, such as sCD89 and transferrin receptor?

4. Is there a rapidly progressively GN (RPGN) variant of IgAN or is this severe hypertensive injury (with or without thrombotic microangiopathy) superimposed on IgAN?

5. Should pathology, in particular the Oxford-MEST-C classification, guide treatment? How do crescents affect treatment decisions? Are there histological thresholds that can guide treatment?

6. In IgA vasculitis, are there biomarkers of renal involvement and prognosis? Should a separate histological classification be considered?

Treatment

7. What is the evidence suggesting renal benefit at a reasonable cost-benefit ratio of established immunosuppressive mono- or combination-therapy (such as steroids, mycophenolate mofetil, cyclophosphamide, azathioprine)? And what is the optimum dosage, dosing intervals, duration of treatment and drug formulation for steroid use in IgAN?

8. What may be the immunosuppressive strategy in patients with lower GFRs? Is there a "point of no return" for IgAN? If so, what is it in terms of eGFR?

9. How should one treat relapses of proteinuria following an initial response to therapy (i.e., supportive or immunosuppressive)?

10. How should one manage nephrotic patients with IgAN without features of minimal change disease (MCD) in the kidney biopsy?

11. Should ethnicity influence treatment decision?

12. Is there a role for tonsillectomy?

Future studies

13. Are there novel emerging immunosuppressive or other approaches (such as rituximab, tacrolimus, enteric corticosteroids, BAFF inhibitor, MASP2 antibody and ACTH) to progressive IgAN?

14. What is the future of clinical trials in IgAN?
    - How can clinical trials be facilitated in the future?
    - Inclusion of high-risk patients only?
    - Appropriate endpoints?
    - Determining optimal time for assessing primary endpoint
      Duration of clinical trial / follow-up
    - Patient reported outcome measures & side effects

Optional questions to address (subject to availability of time since evidence from the literature for these topics is too scarce to warrant incorporation into a guideline)

1. What is the role of complement inhibition in IgAN?

2. What is the role of the gut microbiome in IgAN, and how may dietary or other therapies affect this relationship? What is the role of gluten-free diet in light of an RCT of gluten-free diet being planned in Italy?

3. How should one manage IgAN in the pediatric population?
4. How should one manage recurrent IgAN in the kidney transplant recipient?
5. How should one manage pregnancy in patients with IgAN?
6. Can we formulate recommendations that should be "standard-of-care" (SOC) in all regions and highlight alternative approaches that may be exchanged for SOC in resource-limited countries?

Group 3: Membranous GN (MGN)

Diagnosis

1. Can a diagnosis of MN be made reliably without kidney biopsy?
2. Is a kidney biopsy needed before start of immunosuppressive therapy?
3. Is PLA_2R (antibodies or in biopsy) sufficient to rule out secondary MN? What should be the algorithm for cancer screening?

Biomarkers & prediction of prognosis

4. Which clinical and laboratory parameters predict spontaneous remission?
5. Do antibody assays (PLA_2R, THSD7A) contribute to prediction of spontaneous remission? Should qualitative assays be replaced by quantitative assays? Are epitope-specific assays preferable?

Treatment

6. How should remission be defined?
    a. Are the current definitions of partial remission and complete remission appropriate? Could they be improved?

b. How should anti-PLA_2R be integrated into these definitions?
c. Should other markers be included?

7. What should be the goal of therapy?

8. When should we start immunosuppressive therapy? Which biomarkers are useful in predicting response to therapy? Is kidney biopsy useful as predictor?

9. How should one monitor patients who have developed remission and which parameters should be used to guide restart of immunosuppression?

10. How should one differentiate between proteinuria due to relapse or secondary focal segmental glomerulosclerosis (FSGS)?

11. How should treatment resistance be defined (i.e., non-responsiveness)? What are treatment options for initially non-responsive patients? Is there a role for plasma exchange (PLEX)?

12. Are there new treatment options developed for use in MN? Are there randomized clinical trials or large comparative cohort studies in MN published after 2010 and how should the results change KDIGO treatment guideline? What will be the impact of the MENTOR and STARMEN studies?

13. Should treatment be different in patients with MN and impaired kidney function? What are potential thresholds?

14. How should treatment be adapted in special populations such as in children and pregnant women?

15. How should we manage MN patients who receive a kidney transplant? What is the role of aPLA_2Rab before and after transplantation?

Future studies

16. What is the future of clinical trials in MN?
    - Inclusion of high-risk patients only?
    - Appropriate endpoints?
    - Determining optimal time for assessing primary endpoint
      Duration of clinical trial / follow-up
    - Patient reported outcome measures & side effects
    - Other methodology besides RCTs.

Group 4: Minimal-Change Disease (MCD) and Focal Segmental Glomerulosclerosis (FSGS)

Diagnosis, biomarkers & prediction of prognosis

1. Should FSGS still be considered a single disease entity or rather a family of diseases? Can particular subsets be identified?
   a. Should we abandon "Primary" and "Secondary" FSGS terminology?
   b. Are the terms SSNS and SRNS still relevant?

2. Are there new insights into pathogenesis that can guide treatment in MCD, in particular with respect to permeability factors?

3. What is the role of genetic testing in FSGS? To whom and when should it be applied? Does genetic testing help in choice of therapy?

4. Is histological analysis of renal tissue sufficient for diagnosis and management of FSGS or should molecular diagnosis be incorporated into the routine evaluation of the biopsy to better define the variants that comprise this syndrome?
   a. Do the morphological patterns of FSGS by light microscopy have a role in patient care?

b. Should we recommend biopsy standards for FSGS? (i.e., minimum number of glomeruli to exclude FSGS and who should be re-biopsied?)

Treatment

5. Who should receive immunosuppressive treatment for FSGS and who should not? If needed, what is the most reasonable immunosuppressive approach when corticosteroids have failed?

6. Regarding immunosuppression:
   a. When should therapy with calcineurin inhibitors or cytotoxic agents be considered in MCD?
   b. What about therapy with rituximab, mycophenolate mofetil, adrenocorticotropic hormone (ACTH) or abatacept?
   c. Would one of these therapies be used as first line instead of corticosteroids?
   d. What is the role of plasmapheresis in FSGS?

7. Regarding anti-proteinuric agents:
   a. How do we or should we distinguish immunosuppressive from anti-proteinuric effects of therapies (e.g., steroids, cyclosporine, rituximab, ACTH)
   b. What is the role of angiotensin II/endothelin antagonism in all forms of FSGS?

8. Are there new insights into how we should follow and manage transplanted patients with a history of FSGS? How should we approach treatment of recurrent disease?

9. What are specific aspects regarding the care for pediatric patients?

10. What are specific aspects regarding the care for pregnant patients?

Future studies

11. What is the future of clinical trials in MCD/FSGS?
    - Does it still make sense to study "FSGS" independent of the specific entity?
    - Inclusion of high-risk patients only?
    - Appropriate endpoints?
    - Determining optimal time for assessing primary endpoint
      Duration of clinical trial / follow-up
    - Patient reported outcome measures & side effects

Group 5: Lupus nephritis (LN) and ANCA vasculitis

Diagnosis, biomarkers & prediction of prognosis

1. What is the role of repeating the biopsy, when should it be done, and how often? Is there a role for protocol biopsies in the management of LN? How should we best use the kidney biopsy in relapsing diseases?

2. Is simple histology (light, immunofluorescence, and electron microscopy) of renal tissue sufficient for diagnosis and management of heterogeneous diseases or should molecular diagnosis be incorporated into the routine evaluation of the biopsy? Is the current ISN/RPS classification of LN sufficient?

3. Are proteinuria, urinary sediment analysis and SCr or eGFR sufficient to determine response to therapy? Which criteria should we use to define response to treatment? What about the use of drugs such as calcineurin inhibitors that may alter proteinuria by several mechanisms?

4. a) How can we best apply myeloperoxidase (MPO), proteinase 3 (PR3) for predicting relapse in ANCA vasculitis? Are immune-enzymatic methods equivalent to IF methods when testing for ANCA? Are there other predictive biomarkers that should be incorporated into clinical use, including therapy-specific biomarkers such as B-cell counts in patients treated with anti-B cell

therapies?

b) How can we best apply anti-DNA, complement and extractable nuclear antigen (ENA) profile testing for predicting relapse in LN? Are there other predictive biomarkers that should be incorporated into clinical use, including therapy-specific biomarkers such as B-cell counts in patients treated with anti-B cell therapies? Which approach to consider in serological active (low complement and/or positive anti-DNA) but clinical silent LN patients?

5. Are there any clinical signs or serum/urine biomarkers/genetic tests that can help to:
a. predict who may develop kidney involvement among patients with systemic ANCA and/or help diagnose and direct therapy?

b. predict who may develop LN among patients with systemic lupus erythematosus (SLE) and/or help diagnose and direct therapy?

Treatment

6. Are we using too much corticosteroid in LN and ANCA vasculitis? Can we reduce cumulative dosing? Are short course of intravenous pulse steroids superior to prolonged use of oral steroids?

7. a. For how long should maintenance therapy be continued in vasculitis? When should one consider therapy discontinuation? Should MPO and PR3 positive patients receive different maintenance regimens? Do patients with drug-induced ANCA vasculitis require maintenance?

b. For how long should maintenance therapy be continued in LN? How can patient characteristics (e.g., response to therapy, history of relapse, biomarkers of disease activity) guide length of maintenance therapy? When should one consider therapy discontinuation?

8. How should refractory disease in LN and ANCA vasculitis be defined? What strategies may be used to treat refractory disease? Does induction therapy

differ in patients with ANCA vasculitis when diffuse alveolar hemorrhage is present and/ rapidly progressive renal insufficiency?

9. Which is the role of anti-B cell and other biological therapies in ANCA vasculitis and LN? When to consider anti-B cell therapy in class V LN? What is the role of plasma exchange in crescentic ANCA vasculitis? What is the role of complement inhibition in ANCA vasculitis and LN?

10. Which is the role of antiphospholipid antibodies (aPL) testing in the context of LN? Do aPL and aPL-related nephropathy have an impact on the management of LN? If thrombotic microangiopathy is coexistent with LN on kidney biopsy, what is the appropriate workup and treatment? What is the role of plasma exchange? Anticoagulation? Anti-complement therapies?

11. What is the role of CNI or "multi-target therapy" in the treatment of LN? When to consider to stop CNI?

12. How should LN be managed during pregnancy? When to consider anti-platelet agents?

13. How should disease recurrence for LN/ANCA vasculitis be managed post-transplant?

Future studies

14. What is the future of clinical trials in SLE / ANCA vasculitis?
    - Does it make sense to study particular subgroups? (e.g., separating MPO from PR3; separating class V from Class III/IV LN)?
    - Inclusion of high-risk patients only?
    - Appropriate endpoints?
    - Determining optimal time for assessing primary endpoint
    - Inclusion of pediatric patients in LN trials
    - Duration of clinical trial / follow-up
    - Patient reported outcome measures & side effects

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