Global Action. Local Change.

KDIGO Controversies Conference on Glomerular Diseases

November 16-19, 2017
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 to determine 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 the 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 (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 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? Which other life style modifications are generally advisable?

2. General principles (ii): 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)? Should there be a low GFR cut-off for discontinuing RAAS blockade? 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?

3. Nephrotic syndrome: When to start prophylactic anticoagulant therapy, for how long, and which drugs should be used? (dose?) 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?

4. MPGN (i): Is the division in the histologic classification of MPGN into immune complex-mediated and complement-mediated GN sufficient? If so, what should be the sequence and limit of diagnostic investigation in clinical practice?

5. 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?

6. MPGN (iii): What is the appropriate workup for other variants of MPGN in particular so-called idiopathic MPGN? Which of these variants require immunosuppressive therapy, and what should be used as clinically meaningful endpoints for treatment (e.g., proteinuria/change in GFR)?

7. 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?

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

4. Should pathology, in particular the Oxford-MEST-C classification, guide treatment?

Treatment

5. 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)?

6. What may be the immunosuppressive strategy in patients with lower GFRs?

7. How to treat relapses of proteinuria following an initial response to therapy (supportive or immunosuppressive)?

8. Should ethnicity influence treatment decision?

Future studies

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

10. 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

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?

Biomarkers & prediction of prognosis

4. Which clinical and laboratory parameters predict spontaneous remission?

5. Do antibody assays (PLA2R, THSD7A) contribute to prediction of spontaneous remission? Should qualitative assays be replaced by quantitative assays?

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-PLA2R 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?

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

10. How to 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?

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 guidelines?

Future studies

13. 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?

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?

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. 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?

Future studies

8. 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. How should we best use the kidney biopsy in relapsing diseases? What is the role of repeating the biopsy, when should it be done, and how often?

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?

3. Are proteinuria, urinary sediment analysis and SCr or eGFR sufficient to determine response to therapy? 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 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?

5. Are there any clinical signs or serum/urine biomarkers/genetic tests that can help to: a) predict who may develop LN among patients with systemic lupus erythematosus (SLE) and who may develop kidney involvement among patients with systemic ANCA; b) 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 to 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 (response to therapy, history of relapse, biomarkers of disease activity) guide length of maintenance therapy? When to consider therapy discontinuation?

8. How should refractory disease in LN and ANCA vasculitis be defined? What strategies may be used to treat refractory disease? Which is the role of anti-B cell and other biological therapies? Which is the role of plasma exchange in crescentic ANCA vasculitis? What is the role of complement inhibition?

9. 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 (antiphospholipid syndrome (APS) vs. thrombotic thrombocytopenic purpura (TTP) vs. atypical hemolytic uremic syndrome (aHUS)? What is the role of plasma exchange? Anticoagulation? Anti-complement therapies?

Future studies

10. What is the future of clinical trials in SLE / ANCA vasculitis?
    - Does it make sense to study particular subgroups?
    - 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

REFERENCES

1. Webster AC, Nagler EV, Morton RL, *et al.* Chronic Kidney Disease. *Lancet* 2017; **389:** 1238-1252.

2. Floege J, Amann K. Primary glomerulonephritides. *Lancet* 2016; **387:** 2036-2048.

3. US Renal Data System 2016 Annual Data Report Epidemiology of Kidney Disease in the United States. *Am J Kidney Dis* 2017; 69: S1-S688.

4. Beck LH, Jr., Bonegio RG, Lambeau G, *et al.* M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med* 2009; **361:** 11-21.

5. Birmingham DJ, Merchant M, Waikar SS, *et al.* Biomarkers of lupus nephritis histology and flare: deciphering the relevant amidst the noise. *Nephrol Dial Transplant* 2017; **32:** i71-i79.

6. Parikh SV, Malvar A, Song H, *et al.* Molecular imaging of the kidney in lupus nephritis to characterize response to treatment. *Transl Res* 2017; **182:** 1-13.

7. Sethi S, Theis JD, Vrana JA, *et al.* Laser microdissection and proteomic analysis of amyloidosis, cryoglobulinemic GN, fibrillary GN, and immunotactoid glomerulopathy. *Clin J Am Soc Nephrol* 2013; **8:** 915-921.

8. Rauen T, Eitner F, Fitzner C, *et al.* Intensive Supportive Care plus Immunosuppression in IgA Nephropathy. *N Engl J Med* 2015; **373:** 2225-2236.

9. Fellstrom BC, Barratt J, Cook H, *et al.* Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial. *Lancet* 2017; **389:** 2117-2127.

10. Jayne DR, Bruchfeld AN, Harper L, *et al.* Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis. *J Am Soc Nephrol* 2017. doi: 10.1681/ASN.2016111179.

11. Jones RB, Tervaert JW, Hauser T, *et al.* Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 2010; **363:** 211-220.

12. Stone JH, Merkel PA, Spiera R, *et al.* Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010; **363:** 221-232.

13. ACCESS Trial Group. Treatment of lupus nephritis with abatacept: the Abatacept and Cyclophosphamide Combination Efficacy and Safety Study. *Arthritis Rheumatol* 2014; **66:** 3096-3104.

14. Rovin BH, Furie R, Latinis K, *et al.* Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. *Arthritis Rheum* 2012; **64:** 1215-1226.

15. Thompson A, Cattran DC, Blank M, *et al.* Complete and Partial Remission as Surrogate End Points in Membranous Nephropathy. *J Am Soc Nephrol* 2015; **26:** 2930-2937.

16. Inker LA, Mondal H, Greene T, *et al.* Early Change in Urine Protein as a Surrogate End Point in Studies of IgA Nephropathy: An Individual-Patient Meta-analysis. *Am J Kidney Dis* 2016; **68:** 392-401.

17. Anders HJ, Jayne DR, Rovin BH. Hurdles to the introduction of new therapies for immune-mediated kidney diseases. *Nat Rev Nephrol* 2016; **12:** 205-216.