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KDIGO Controversies Conference on the Role of Complement in Kidney Disease

Scope of Work

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 may lead to guidelines in the future.

BACKGROUND

In 2015, KDIGO convened a Controversies Conference on two prototypical complement-mediated kidney diseases: atypical hemolytic uremic syndrome (aHUS) and C3 glomerulopathy (C3G). Literature has since emerged indicating a role of complement in the etiology of a broader range of kidney diseases, including diabetic kidney disease and a number of glomerulonephritides. As many experimental therapies targeting complement are now under investigation for kidney diseases beyond aHUS and C3G, KDIGO recognizes the need for a conference to address the expanding role of complement in the pathophysiology, diagnosis, management, and treatment of various glomerular diseases, nephropathies in the setting of diabetes, and other forms of HUS. This conference also provides an opportunity to revisit the literature that has accumulated to date on aHUS and C3G and assess whether the guidance outlined in the 2015 conference report requires updating.



CONFERENCE OVERVIEW

This KDIGO conference will gather a global panel of multidisciplinary clinical and scientific expertise (i.e., pediatrics, rheumatology, complement basic research, renal pathology, genetics) and a motivated group of patient representatives to define the role of complement in a spectrum of kidney diseases including glomerular disorders and diabetic nephropathy. For each disease that will be addressed, the evidence indicating whether complement plays a primary or secondary role in their etiologies will be reviewed. The value of biomarkers of complement activity in monitoring disease course and whether specific drivers (i.e., genetic or acquired) dysregulate complement activity will be critically examined, as will the potential impact/role of the glomerular microenvironment in contributing to the complement response. This meeting will also explore whether any anti-complement therapies currently under investigation may be potential treatments for this spectrum of kidney diseases. We will also re-evaluate current evidence to identify relevant new data to guide management of renal conditions with established complement dysregulation, i.e. aHUS and C3G.

This Controversies Conference will specifically focus on diabetic nephropathy,¹ focal segmental glomerulosclerosis (FSGS),²⁻⁴ systemic vasculitides (lupus nephritis, anti-neutrophil cytoplasmic antibody (ANCA)-associated renal vasculitis, anti-phospholipid-antibody syndrome [APS]),⁵⁻⁷ classic primary glomerular diseases (IgA nephropathy, membranous nephropathy),⁸⁻¹² post-infectious glomerulonephritis,¹³ immune-complex membranoproliferative glomerulonephritis (IC-MPGN)/complement 3 glomerulopathy (C3G),¹⁴⁻¹⁶ and different forms of thrombotic microangiopathies (TMAs).¹⁷ It will purposefully not cover the potential role of complement in acute kidney injury, transplant rejection, and dialysis, which is considered beyond the scope of the current charge.

The conference will include patients/caregivers to gain the unique perspective they provide on patient-centered challenges, values, and preferences associated with these diseases as they relate to diagnosis, prognosis, management, and treatment.

Drs. Richard Smith (University of Iowa, USA) and Marina Vivarelli (Bambino Gesù Pediatric Hospital IRCCS, Italy) will co-chair this Controversies Conference. The format of the conference will involve topical plenary session presentations followed by focused



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discussion groups that will report back to the full group for consensus building. This highly interactive conference will invite key thought leaders and relevant stakeholders (including patients) in nephrology and other related disciplines who will comprehensively review the literature and current state of understanding in this area and address clinical issues as outlined in the **Appendix: Scope of Coverage**. The conference output will include publication of a position statement that will help guide management and future research.



APPENDIX: SCOPE OF COVERAGE

Breakout Group 1: Diabetic Nephropathy and FSGS

Diabetic Nephropathy: Pathogenesis

1. What is the evidence (from genetic associations, biomarker data, and animal models) that complement is activated in diabetic nephropathy?
2. Is complement activation causally related to disease development in diabetic nephropathy or is it a result of glomerular injury?

Diabetic Nephropathy: Complement Biomarkers

3. Should complement-related biomarkers be part of the work-up for diabetic nephropathy? If yes, which? What is the prognostic value of these biomarkers?

Diabetic Nephropathy: Treatment

4. Is there a role for therapeutic complement inhibition in diabetic nephropathy?
5. Who should be considered for complement inhibitor therapy? Should it be disease stage specific? Do we have biomarkers of response to treatment?

FSGS: Pathogenesis

6. What is the evidence (from genetic associations, biomarker data and animal models) that complement is activated in FSGS?
7. Is complement activation causally related to disease development in FSGS or is it a result of glomerular injury?
8. Which forms of FSGS are more likely to be causally driven by complement activation?



FSGS: Complement Biomarkers

9. Should complement-related biomarkers be part of the work-up for FSGS? If yes, which?
10. What is the prognostic value of these biomarkers?

FSGS: Treatment

11. Is there a role for therapeutic complement inhibition in FSGS? In what forms of FSGS is complement inhibition most likely to be beneficial?
12. Who should be considered for complement inhibitor therapy? Should it be disease stage specific? Do we have biomarkers of response to treatment?



Breakout Group 2: Lupus, Anti-Phospholipid Syndrome (APS), and ANCA-Associated Vasculitis (AAV)

Thrombosis Associated with APS

1. Is increased complement activity involved in the pathogenesis of both venous and arterial thrombosis?
2. Is it helpful to measure complement-related biomarkers (e.g., C5b-9, C3a, C5a, C4a, C4d, Ba, Bb, etc) in APS?
3. What insights can be gained from complement C5 inhibition in catastrophic APS?
4. Would modifying complement activity interfere with the mechanism of action of currently used anti-thrombotic agents?
5. What are the risks of complement inhibition in APS?
6. How would complement inhibition be tested in APS?

Lupus Nephritis

7. What is the contribution of complement activity to kidney injury in relation to the other effector mechanisms active in lupus nephritis? Is complement activation a driver of kidney injury or a consequence of immunoglobulin deposition in the kidney?
8. Is complement activity a driver of non-renal lupus lesions?
9. What is the place for anti-complement protein antibodies in lupus nephritis (e.g., anti-C1q antibodies); are they useful biomarkers with relevance for diagnosis and prognosis?
10. What is the relevance of the link between complement deficiencies and lupus (the “systemic lupus erythematosus [SLE] paradox”)?



11. Is it useful to measure complement activation biomarkers (e.g., C5b-9, C3a, C5a, C4a, C4d, Ba, Bb, etc) and where (e.g. plasma, urine, kidney biopsy)? Could novel approaches (transcriptomics, multiplex imaging) provide more information?
12. What insights can be gained from complement C5 inhibition in lupus nephritis?
13. Would modifying complement interfere with the mechanism of action of currently used treatments in lupus nephritis?
14. What are the risks of complement inhibition in lupus?
15. How would complement inhibition be tested in lupus nephritis?

ANCA-Associated Vasculitis (AAV)

16. What have we learned from use of avacopan in AAV?
17. Is it useful to measure complement activation biomarkers (e.g., C5b-9, C3a, C5a, C4a, C4d, Ba, Bb, etc) and where (e.g. plasma, urine, kidney biopsy)?
18. Is there a role for targeting other parts of the complement system (e.g. C3) in AAV?



Breakout Group 3: IC-MPGN, C3G, and Postinfectious Glomerulonephritis (PIGN)

Genetic Testing

1. What are the indications for genetic or genomic testing in patients with IC-MPGN, C3G, PIGN?
2. How should complement gene variants of undetermined significance in patients with C3G be interpreted in the clinical setting? Is there a role for identifying non-monogenic (i.e. common) genetic risk factors for C3G in clinical practice?
3. Which genes should be included in comprehensive genetic testing by clinical laboratories for the work-up of C3G and IC-MPGN? What is the role of genetic testing in the clinical management of these diseases, including in the setting of renal transplantation and in the choice of living related donors?

Nephritic Factor (NeF) Testing

4. Which is (are) the best assay(s) for NeFs?
5. How can we organize a standardization of NeF testing?
6. NeFs are a very heterogenous group of antibodies (C3NeF, C5NeF, C4NeF). What is the impact of each on disease pathogenesis, disease classification and clinical outcome of IC-MPGN, C3G, PIGN?

Other Serological Tests

7. What is the prevalence of anti-factor H, anti-factor B, and anti-C3b antibodies in IC-MPGN, C3G, and PIGN, and what is the utility of assays for each in clinical practice and in monitoring response to therapy?
8. Are there other emerging serologic markers?



Treatment of C3G, IC-MPGN, PIGN

9. Which is the current best approach to treatment of C3G and IC-MPGN?
When should complement inhibition be considered?
10. Should C3G and IC-MPGN be considered equivalent with respect to complement inhibiting therapies?
11. Which endpoints of response to treatment should be employed?
12. Which biomarkers, both serological, urinary and on the kidney biopsy, may be helpful in monitoring effectiveness of complement inhibition in C3G and IC-MPGN?
12. Do we have enough information to tailor the choice of complement inhibitor based on the serological, genetic and biomarker work-up of patients with C3G and IC-MPGN?
13. Is there a role for complement inhibition in PIGN?

Monoclonal Gammopathies

14. Which patients presenting with C3G/MPGN should be tested for a monoclonal gammopathy? Which tests should be performed to identify/exclude a monoclonal gammopathy in these patients?
15. Is C3G-monoclonal gammopathy of renal significance (MGRS) an indication for treatments targeting a hematological clonal abnormality?
16. Is there a role for complement inhibition in this condition?



Breakout Group 4: IgA Nephropathy (IgAN), Immunoglobulin A–Associated Vasculitis (IgAV) With Nephritis, and Membranous Nephropathy (MN)

IgAN and IgAV With Nephritis: Disease Pathogenesis

1. What is the evidence (from preclinical models and human and genetic studies) that complement activation plays a role in kidney injury in IgAN/IgAV with nephritis?
 - a. What is the role of the alternative pathway?
 - b. What is the role of the lectin pathway?
2. For each disease and each pathway, is complement-mediated injury a primary driver of disease or a generic downstream consequence of glomerular immunoglobulin deposition?
3. In what way, if any, does the role of complement activity differ between IgAN and IgAV with nephritis?

IgAN and IgAV With Nephritis: Biomarkers

4. Are there data to support the use of complement-associated biomarkers to inform prognosis, treatment selection, or monitoring of response to treatment in IgAN/IgAV, including circulating biomarkers, urinary biomarkers and kidney biopsy immunofluorescence stains (C3, C4, C1q, others) as well as novel biomarkers?

IgAN and IgAV With Nephritis: Treatment

5. What is the evidence that complement inhibition in IgAN/IgAV is safe and efficacious, and when should a complement inhibitor be used—for induction,



maintenance of remission, or lifelong? What is the evidence to indicate which pathway should be targeted?

MN: Disease Pathogenesis

6. What is the evidence (from preclinical models and human and genetic studies) that complement activation plays a role in kidney injury in membranous nephropathy?
 - a. What is the role of the alternative pathway?
 - b. What is the role of the lectin pathway?
7. In different forms of MN, is complement-mediated injury a primary driver of disease or a generic downstream consequence of glomerular immunoglobulin deposition? Is there a difference in the role of complement depending on the antigen involved (i.e. PLA2R vs other identified antigens vs no identified antigen)? Is there a role for complement in secondary forms of membranous nephropathy?

MN: Biomarkers

8. Are there data to support the use of complement-associated biomarkers to inform prognosis, treatment selection, or monitoring of response to treatment in MN, including circulating biomarkers, urinary biomarkers and kidney biopsy immunofluorescence stains (C3, C4, C1q, others) as well as novel biomarkers?

MN: Treatment

9. What is the evidence that complement inhibition in MN is safe and efficacious? When should a complement inhibitor be used—for induction, maintenance of



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remission, or lifelong? What is the evidence to indicate which pathway should be targeted?



Breakout group 5: Complement-Mediated Forms of HUS.

1. What is the definition and the spectrum of complement-mediated forms of HUS? Is the current terminology “atypical HUS” accurate, or does it need updating? If updating is needed, what is a preferable alternative? Is the term “complement-mediated forms of HUS” useful and adequate?
2. Which complement pathways—and to what extent—are involved in complement-mediated HUS? Are pathways other than complement involved in the pathogenesis of complement-mediated HUS?
3. Is it possible to distinguish complement activation/dysregulation in different forms of HUS as transient versus permanent? Can this distinction be helpful in classification and management of HUS?
4. What biomarkers and/or tests are helpful to diagnose and monitor complement-mediated forms of HUS?
5. How should the results of complement genetics (common and rare variants, copy number variation, etc...) and tests for acquired autoantibodies (i.e. anti-factor H autoantibodies) be reported and interpreted?
6. How do genetic results and test for acquired autoantibodies (i.e. anti-factor H autoantibodies) impact on the management of complement-mediated HUS, including in the setting of renal transplantation and in the choice of living related donors?
7. Does the renal microenvironment contribute to the pathogenesis of renal involvement in complement-mediated forms of HUS?
8. What is the optimal use of current therapies and what are the emerging therapies for complement-mediated HUS?



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9. When and how should complement inhibition be discontinued in complement-mediated HUS?
10. Is there a role for complement inhibition in STEC-HUS?
11. Is there a role for complement inhibition in other forms of HUS (i.e. HUS post-bone marrow transplant, pregnancy-associated HUS, etc.)?



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