KDIGO Controversies Conference on Role of Complement in Kidney Disease
- Public Review Comments -

As of August 17, 2022
Industry comments are highlighted in blue

General comments:

Fabrizio Spoleti (Progetto DDD Onlus):

I reviewed the Scope of Work and in my opinion it is complete, appropriate and exhaustive.

Heather Reich (University of Toronto):

I think that a discussion regarding global accessibility to novel testing and therapies is imperative. The costs of many of the treatment approaches are prohibitor /sic/ and unsustainable even in countries where typically health care is covered by government agencies. Emerging treatment options (not just complement-related) in GN are extremely exciting. However, lack of accessibility is going to be the next global challenge. Even in Canada, I do not see the multi-target pharmaco approaches as being accessible within a sustainable and equitable healthcare system.

Peter Barany (Karolinska Univ Hosp and Karolinska Institutet):

I think the Scope of Work is comprehensive. My only comments are that it would be good to have a group of clinical chemists, immunologists and pathologists to scrutinize the laboratory methods used in this complex area. The need for standardisation and the clinical value of the methods used are important issues. It is also important to include other relevant specialists like hematologists, infectious specialists and obstetricians etc in the conference.

Mona Alrukhaimi (Emirate Nephrology society):

It looks perfect and covers all the possible aspects but if possible to add what is the difference among the various anti complement therapy available.

Ratna Samanta (McGill University):

Will there be any discussion on the ease/accessibility for physicians to be able to order the various complement tests (currently rather prohibitive to order)?

Proper frequency of assessing complement inhibitors/drivers to assess clinical response

Maria José Soler Romeo (Hospital del Vall d´Hebron):
Thank you for bringing all of these pathologies involved in the complement together.
In my opinion the Minimal Changes Diseases GN is lacking in the scope, maybe it can be added.

Suparna Mallik (Novartis):

Suggestions to include the following questions and/or topics (not disease specific):

1. Discussion points regarding the patient journey/patient reported outcomes: What patient factors are important to consider when selecting complement inhibition therapies? Is symptom reporting, approaches in diagnosis (i.e., biopsy), preferences in treatment routes of administration, and treatment compliance discussed when determining therapeutic regimens?

2. What is the role of repeat (post-baseline) biomarkers for treatment monitoring or efficacy? Do biomarkers serve as a valuable aid during initial diagnosis of complement mediated kidney diseases (CMKDs)?

3. Suggest discussing during all breakouts: Is it valuable to measure complement activation biomarkers (i.e., C5b-9, C3a, C5a, C4a, C4d, Ba, Bb)? What is the best way to measure complement activation biomarkers – via plasma, urine, biopsies, or other modes?

4. What are examples of exploratory prognostic biomarkers that warrant future research?

5. Could novel approaches such as transcriptomics and multiplex imaging provide valuable information on how pathogenesis of CMKDs may be driven by complement activation?

6. Suggest discussing during all breakouts: Which parts of complement are activated – AP, CP, LP? We suggest probing as different CMKDs have varying components of the pathways and/or pathways activated. Levels of AP, LP, CP activation may also differ among CMKDs.

7. Should vaccination against encapsulated bacteria be suggested for patients with glomerulonephritis?

8. Suggest including questions on pediatric needs re: treatment as well as caregiver burden.

Peter Zipfel (University Professor Leibniz Institute for Natural Products Research and Infection Biology, Jena, Germany):

Additional topics to include in the discussion:

- Individual disease profiles, what is the complement status for each disease
- Aim for new assays for complement and for complement biomarkers
- Testing biomarker combinations
- Contribution of the special glomerular cell types for kidney pathologies
- Role of proteomics
- Acute vs chronic disease progression
- How relevant are autoantibody levels in DEAP- HUS
- Role of *S. pneumoniae* and infection triggered HUS
- Relevant - monitor effect of complement therapies
- Alternative routes of complement activation: Kallikrein, Proteases

Rating of Disease relevant gene variants:
Rank variations:

- True genetic variants,
- likely genetic variants,
- variants of potential relevance,
- variants of no significance -polymorphisms
- Which genetic variants are pathologic, which combinations of genetic variants are pathologic
- Search for new, relevant genes involved in each disease

Additional Issues:

- Role of each complement activation pathways in a given clinic setting
- Biomarkers which allow to monitor effect of treatment
- Contribution and importance of the amplification loop
- PLA (proximity ligation assay) allows to monitor and quantitate the AP and CP/LP complement convertases in situ in glomerular and other tissue biopsies
- Treatment in a disease setting: how long and when to stop
- Are the diseases discussed homogenous entities with common parameters, or do they represent different spectral forms of each disease?
- How is the glomerular cell type affected by a given pathologic factor, how does each cell type contribute to disease pathology?
- Are endothelial cells, mesangial cells, podocytes identical or different in terms of complement sensitivity
- Do the cells have different expression levels of membranous bound complement regulators and do they show different susceptibility to complement?
- Is proximal, middle or distal complement relevant for the specific disease pathology
- Which effector branch/arm of complement contributes or contributes most to disease pathology

Vasculitis UK:

Thank you for giving us an opportunity to comment on the scope of work – we represent the interests of people with living with several of the diseases relevant to this conference. We will not be able to attend the meeting face to face due to ongoing concerns regarding COVID in immunosuppressed people as well as cost. We do hope there truly is a patient voice in the room so your aims can be met.

Whilst most of the meeting will focus rightly on the science of complement and disease mechanisms we do want to feedback on some specific elements very relevant to us and our members.

(1) Access to care – this is a global meeting and we would ask that within each section there is consideration of how to ensure access to diagnostic testing, clinical expertise and treatment. We know our own members struggle sometimes within one country and services can be patchy and diagnosis delayed. How can this improve? How can testing be more available? Are there at risk groups of people who need to be focused on? How do you work to ensure roll out in lower income countries? Are you actively considering specific areas of disparity eg ethnic origin, gender and deprivation?
(2) Genetic testing – we ask that this is considered carefully and all concerns listed to – what are potential implications for the patient and other family members? Will this be available everywhere?
(3) Education for physicians – our members often have delayed diagnosis and many of these diseases are rare – how will you work to deliver education to primary care physicians and non-expert secondary care physicians? This is very important for us – it sometimes seems we are the ones educating our own doctors! Please consider this as a workstream for the meeting – if it is not, the work is wonderfully academic but not disseminated to the physicians managing the patients with the diseases.
(4) Patient reported outcomes and experience – please consider this throughout the conference especially over importance of symptoms and how they are measured and considered in clinical practice. We are always concerned over the burden of disease and its treatment – corticosteroids are a major problem and please consider how their impact is measured in practice and steps to avoid or keep dose low as possible. How should physicians assess key patient outcomes in practice in these diseases? What measures should be used in clinical trials? How can new drugs be assessed after approval for their impact on patient reported outcomes and experience? Clinical outcomes and parameters are measured and often have to be reported as part of FDA or EMA requirements but should patient outcomes also be routinely gathered as well?
(5) Information for patients and their carers – these are complex diseases and concepts but the group needs to consider how it can better deliver information to patients and their carers. How will you explain testing? How can you explain the complement system and help patients understand its role in their disease and how a new drug works? This is a

real challenge - please develop a plain language summary of this conference output so patients with the diseases can read and understand. They then can even discuss with their own doctors – see (3) above.

We hope our comments can be reviewed and considered and we sincerely hope that there are patient voices in the room during the discussions. We would be delighted to support more and review other material.

Vincenzo Montinaro (Ente Ecclesiastico Ospedale Generale Regionale "F. Miulli" - Acquaviva delle Fonti (BA), Italy):

Analysis of the role of Complement proteins (C3, C4, fB, H) produced locally in kidney tissue in promoting or regulating pathogenic factors involved in both glomerular and tubulo-interstitial patterns of kidney damage.

Andreas Kronbichler (Department of Medicine, University of Cambridge):

Another issue is the measurement of other complement components rather than C1q, C3(c) on kidney biopsy specimens. A disease of relevance here is also anti-GBM disease with clinical efficacy of eculizumab in some cases (34622110), and some studies showing complement regulation in blood (22941511) and kidney specimens (24658070).

Group 1: Diabetic Nephropathy and FSGS:

Anuja Java (Washington University school of medicine in St. Louis, MO, USA):

I have a couple thoughts:
1) For FSGS, IgA and Lupus, it would be helpful to try and specify how to tease out the role of complement when TMA is associated with these conditions?

2) Under biomarkers, clarifying how urinary biomarkers for complement compare to blood and if they have a role in any of the diseases?

Suparna Mallik (Novartis):

Diabetic Nephropathy: Pathogenesis

Add:

3. *What co-morbid conditions may increase complement activity in diabetic nephropathy?*

FSGS: Pathogenesis

7. Is complement activation causally related to disease development in FSGS or is it a result of glomerular injury? *Does the distinction matter with respect to the development of therapeutics?*

Asher Schachter (Visterra, Inc.):

Wonderful agenda, I'm looking forward to the discussions. I have a few comments on the scope- apologies if these are tangential to the intended focus...

For Breakout Group 1 (specifically re:FSGS), I think it would be helpful to discuss if and how the role of complement differs between specific FSGS populations, namely idiopathic/steroid responsive FSGS/MCD spectrum vs. secondary causes of FSGS (obesity, hypertension), vs. genetic/familial FSGS.

Group 2: Lupus, APA Syndrome and AAV:

Anuja Java (Washington University school of medicine in St. Louis, MO, USA):

I have a couple thoughts:
1) For FSGS, IgA and Lupus, it would be helpful to try and specify how to tease out the role of complement when TMA is associated with these conditions?

2) Under biomarkers, clarifying how urinary biomarkers for complement compare to blood and if they have a role in any of the diseases?

Andreas Kronbichler (Department of Medicine, University of Cambridge):

The Appendix and the Scope of Coverage is well taken and there is not much to add. I am very glad to be able to participate.

- One issue that remains with the approval of avacopan in most countries is its specific use and the price in comparison to the comparator. If you consider eculizumab or ravulizumab are used without alternative avacopan has one, namely steroids. Discussions should also focus on specific patient groups, which likely benefit the most of the therapy. The updated EULAR recommendations 2022 (unpublished) have focused a bit on this topic.

If needed, I am more than happy to cover one of the sections (especially AAV, but also others are possible).

Juan Mejia-Vilet (Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran):

I believe this conference should incorporate discussions over renal thrombotic microangiopathy lesions in systemic lupus erythematosus (TMA-SLE). Although many physicians believe that renal TMA-SLE is only caused by antiphospholipid syndrome (antiphospholipid syndrome nephropathy - APSN), renal TMA-SLE may be caused by several etiologies as now incorporated in the KDIGO 2021 GN Guidelines. In fact, in two of the "largest" series to date (Song Di - Arthritis Car Res 2013 & Mejia-Vilet JM Clin Rheumatol 2021), most cases corresponded to complement-mediated TMA (negative antiphospholipid antibodies, normal ADAMTS13 activity, and evidence of complement activation). This etiology may be somehow similar to aHUS (genetic predisposition or acquired?).

Discussions about this topic are needed to clearly define the approach and treatment for renal TMA-SLE. A first approach is now included into the KDIGO 2021 GN guidelines, but there is a need for better understanding and study of this etiology. Furthermore, complement-mediated renal TMA may be a candidate for treatment with complement inhibitors.

Our group demonstrated that the plasma and urine levels of complement activation products (especially those of the alternative pathway) increase at flare, and then decrease after treatment (Clin Rheumatol 2021). These results need to be reproduced in other studies, but suggest that complement fragments may serve as biomarkers in renal TMA-SLE.

Suparna Mallik (Novartis):

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?

We suggest separating this question. Perhaps the second part of the question can be on its own/not linked to the first part:

7. What is the contribution of complement activity to kidney injury in relation to the other effector mechanisms active in lupus nephritis?

8. Is complement activation a driver of kidney injury or a consequence of immunoglobulin deposition in the kidney?

13. Would modifying complement interfere with the mechanism of action of currently used treatments in lupus nephritis? *How would complement inhibition fit into current treatment paradigms (i.e., induction versus maintenance treatment)?*

ANCA-Associated Vasculitis (AAV)

18. 1. Is there a role for targeting other parts of the complement system (e.g. C3, *a specific pathway*) in AAV?

Asher Schachter (Visterra, Inc.):

For Breakout Group 2, it would be helpful to discuss if and how physicians are using avacopan, i.e. what clinical scenario(s) prompt treatment initiation, timing vs. dosing with anti-CD20 (rituximab), and what endpoints are generally used to determine whether the patient is responding to avacopan.

Ronald Taylor (University of Virginia School of Medicine):

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

Thrombosis Associated with APS

1. In APS, venous thrombosis is twice as common as arterial thrombosis, but anecdotal descriptions of both syndromes implicate complement in their pathogenesis [1-3]. For example, Brodsky's group has made use of a modified Ham test [4] to examine the complement activating potential of sera taken from patients with APS or CAPS [5, 6]. Positive sera mediate complement-dependent killing of indicator cells. They found that 36% of patients with thrombotic APS and 6 of 7 patients with CAPS had positive sera. Two of the CAPS patients had arterial thrombosis, and 1 of them had positive sera. They also report that the transition from APS to CAPS appears to be mediated by "a second hit" of complement. That is, individuals with APS can have autoantibodies with up to 3 different specificities [7-9]. These include lupus anticoagulants, antibodies specific for phospholipids, and antibodies specific for beta glycoprotein I. However, if these individuals also have additional (and rare) mutations that enhance complement activation, this will increase complement activation mediated by these autoantibodies, thus likely presaging CAPS [5, 6].

The critical role of complement in thrombosis in APS (either arterial or venous) is supported by several reports that include animal models [7, 8, 10].

Additional evidence that complement mediates venous and arterial thrombosis is derived from several case reports that eculizumab therapy was able to suppress or reverse disease pathology in individuals with venous or arterial thromboses [2, 11-13]. However, reports of the successful use of eculizumab "may be greatly exaggerated" (borrowing from Mark Twain). Yelnik et al. have reported that patients with CAPS "respond inconsistently to eculizumab", and this may constitute a real problem in terms of take home lessons for therapies [14]. As noted by these authors, "poor outcomes are less likely to be reported."

2. Based on these considerations, careful and comprehensive complement measurements at baseline as well as during disease activity could be quite useful in helping to predict disease course. In view of Brodsky's report, it may be more important to block the classical pathway than the alternative pathway, and this could be revealed based on measures of, for example, C4a versus Bb. If an increase in a specific marker were to presage enhanced disease activity, this would be very useful and important in terms of planning therapies. However, a practical question must focus on whether these measurements can be made multiple times during a patient's disease course to allow for definitive determinations that can correlate complement activation with disease activity.

3. As noted above, several reports indicate eculizumab treatment may be quite effective. Questions of the timing of treatment and degree of disease pathology before treatment is started must be considered. In addition, under these conditions comprehensive complement assays during a crisis and immediately before eculizumab treatment (inexpensive compared to the cost of eculizumab) could also be quite informative and have the potential to identify individuals most likely to benefit from C5-directed therapy.

4. Anti-coagulants including Vitamin K antagonists are the major anti-thrombotic agents used [1, 3, 8, 15]. Complement-based therapies should not interfere here.

5. Chronic complement inhibition will increase the risk of infection [11, 16] and prophylactic vaccinations should be included.

6. It may be necessary to identify patients with APS who also have the "second hit" identified by Brodsky (susceptible to increased complement activation). These are the APS patients who should first be considered for complement-based therapies. It still might be too expensive to conduct trials with prophylactic eculizumab, but trials with drugs that block C3 activation (compstatin or Pegcetacoplan) seem more reasonable [17]. Although oral inhibitors of Factor B and Factor D are under development [18-20], based on Brodsky's work targeting of the AP of complement may be less effective.

Lupus Nephritis

7. In 1979 Swaak and colleagues reported that substantial disease activity and in particular renal involvement in lupus was correlated with sharp declines in the titers of anti-dsDNA antibodies that appeared coincident with decreases in the concentration of circulating complement components C1q and C3 [21]. These observations are quite consistent with the idea that dsDNA was released into the bloodstream and this was rapidly followed by the formation and deposition of complement-fixing dsDNA/anti-dsDNA immune complexes in the kidney. These findings do not allow for a differentiation between the inflammatory properties of the immune complexes compared to inflammation mediated by complement activation. Under these conditions it is not possible to determine if the immune complexes activate complement before or after (or simultaneously) they deposit in the kidney. However, we have

demonstrated in a non-human primate model that dsDNA/anti-dsDNA immune complexes form rapidly in the circulation, activate complement, capture C3b, and bind to erythrocytes via CR1 [22-25]. Therefore it is likely that the immune complexes can form and activate complement before they deposit in the kidney.

8. Several lines of evidence indicate that in lupus, complement also plays a role in producing lesions in the lung and the heart [26-29]. In particular, deposition of complement components in the heart and lungs of lupus patients has been reported and is correlated with clinical activity. Moreover, adverse pregnancy outcomes in lupus have been attributed to complement activation [30]. Also of note, Meridor and colleagues have found that IVIG can be used to treat acute cardiomyopathy in patients with lupus [31]. As noted below, the mechanism of action of IVIG in the treatment of immune complex disease remains uncertain, but the success of the treatment suggests it may well be associated with either suppression of complement or neutralization of the action of effector cells expressing Fc receptors.

9. The aberrant immune responses in lupus appear to be initiated based on cellular debris/apoptotic cells that are not properly eliminated and therefore induce autoantibody formation [10, 32, 33]. C1q could then bind to these structures and become "immunogenic." The appearance of C1q autoantibodies is likely downstream of the initiation of disease activity in lupus [16], and it is not clear that following C1q antibodies can provide useful information, as only about 1/3 of lupus patients have C1q autoantibodies [33].

10. C1q, C4, and C2 all play important roles in the proper handling and rapid disposal of cellular debris/apoptotic cells, and in their absence (or when expressed at lower than normal levels) the "uncleared" debris is immunogenic [10, 18, 32-35].

11. As discussed by Fakhouri et al., these measures, at all sites, have great potential to allow for "a clear demonstration of the clinical impact of these complement biomarkers on the severity and outcome of kidney disease" [36].

12. In cases of SLE associated with TMA, C5 inhibition is quite reasonable, and it has been demonstrated to be effective in some cases [18, 37]. The impetus for this therapy derives from the finding that C5 inhibition with eculizumab is effective for treating TMA associated with aHUS. Sporadic reports suggest that eculizumab may also be effective in treating glomerulonephritis in lupus [18, 38-40]. It would be quite informative to conduct trials that compare the efficacy of eculizumab in treating lupus associated with TMA versus treating lupus associated with glomerulonephritis.

13. Based on the review by Li et al [18], complement inhibition is unlikely to have negative impacts on the usual anti-inflammatory/immunosuppressive agents (glucocorticoids (GC), mycophenolate mofetil, cyclophosphamide, cyclosporin A) used to treat lupus.

14. Infection is clearly a major risk factor for chronic complement inhibition in lupus [11, 16]. In view of the fact that complement titers can be reduced due to disease activity in lupus, complement inhibition may increase the risk of infection.

15. Pegcetacoplan has been approved for treating PNH [17]. Therefore it would be reasonable to use it "off label" to treat lupus patients who have ongoing complement activation (revealed in the circulation by increased levels of C3a/C5a, C5b9). Trials with this agent, or with eculizumab, could be conducted and patients monitored with kidney function tests, complement component assays and kidney biopsies after 6 months of treatment.

ANCA-Associate Vasculitis (AAV)

16. Avacopan has clearly demonstrated efficacy, slightly better than GC, in AAV [41, 42]. This confirms that complement is clearly playing a substantial role in AAV pathology. However, there are other pathways, probably independent of complement that likely lead to tissue damage as well, and suggestions for strategies to target these pathways are discussed (see below).

17. Based on the results of the avacopan trials, a focus on C5a and C5b9 in plasma and urine would be most important. Does avacopan-mediated inhibition of C5a receptor activation on neutrophils and monocytes reduce the "vicious cycle" [43, 44] of generation of inflammatory products released from these cells? That is, can avacopan therapy lead to inhibition of the production of C5a and C5b9? The effects on C4a are unlikely to be evident, as it is the AP that appears to be most important in AAV.

18 Yes, other elements of complement and other effector functions should also be targeted in AAV (see below).

Is there a role for targeting other inflammatory systems that are directly or indirectly related to autoantibodies, immune complexes and complement that likely play a role in these kidney diseases?

As noted by Bao et al, "The involvement of the complement system in the pathogenesis of SLE is well accepted; yet its exact role is not clear" [32]. Walport has stated that "it is not straightforward to treat SLE by the manipulation of the complement system" [33]. Deposition of virtually all complement components in the kidney clearly leads to substantial injury, as reported or reviewed by numerous investigators [33-35, 45, 46], However, the work of Clynes and Ravetch [47] in an SLE mouse model continues to confound our understanding: They reported that when they knocked out the gamma chain of the Fc receptor of NZB/W (lupus model) mice, the mice were protected from severe nephritis, although immune complex and complement deposition in the kidneys continued as in the wild-type mice. This observation emphasizes the importance of also considering the inflammatory properties of immune complexes that are independent of complement and are mediated by Fc gamma chain receptors on effector cells such as neutrophils and macrophages [10, 33, 48]. Based on these

considerations, several combination strategies for treating APS, lupus, and AAV should be considered.

APS, lupus, and AAV are all characterized by the emergence of complex autoantibodies that appear to target more than one autoantigen [16, 45, 48]. In all three of these diseases there is compelling evidence that complement plays an essential role in pathogenesis [10, 32, 36]. However, it is important to keep in mind, that, as noted below, several similar pathologies appear to be operative simultaneously in these maladies, and it is unlikely that a single agent that targets one step in the complement cascade will be adequate to treat these diseases [36, 48, 49]. For example, with respect to AAV, Massicotte-Azarniouch et al. [50] have stated that "ANCA vasculitis pathogenesis is a multi-step process with multiple potential triggers, implicating multiple different cell types. Combination therapies will likely remain essential for induction of remission of active ANCA vasculitis."

The level of complexity is illustrated based on the outcome of treatment of PNH with eculizumab: There are actually two mechanisms that destroy erythrocytes in PNH. Eculizumab only blocks the downstream lytic step, which is based on the activation of complement component C5 followed by generation of the membrane attack complex [17]. However, in about 1/3 of the PNH patients, C3d-opsonized erythrocytes are also removed by extravascular phagocytosis, and in this case targeting of the C3-opsonization step with Pegcetacoplan increases the efficacy of eculizumab. Indeed, it may turn out that reagents that target C3 activation will prove to be a very effective single therapy, but it should be noted that initially it appeared that eculizumab alone, by targeting a single step, would provide a fully effective therapy for all PNH patients. As noted above, use of avacopan to block C5aR1 constitutes a novel therapy for AAV that is slightly better than immunosuppression mediated by GC, and it is also advantageous because it has far fewer side effects that GC therapy. However, it must be emphasized that after one year, avacopan is effective in only 66% of the treated patients. It is also not clear how long-lasting this therapy will be, but there is clearly room for improvement. An obvious and difficult question, is why is avacopan effective in only 66% of the treated patients? What additional pathway or target is being overlooked?

On this basis there are several alternative strategies that can be considered in the treatment of APS, lupus, and AAV that have the potential to add to the efficacy of therapies based on targeting complement alone. There are several similarities in pathologic mechanism in APS, lupus, and AAV. Although the role of neutrophils in AAV has been clearly demonstrated, it should be noted that neutrophil extracellular traps (NETS) constitute important pathogenic factors in AAV and in fact it has now been demonstrated, in a voluminous literature, that they play similar roles in the pathologies of APS and lupus [15, 16, 49, 51-58]. These structures contain DNA that is released from activated neutrophils, and increasing evidence indicates that these NETS (which normally serve a defensive role against bacteria) can induce substantial pathologies including thromboses in local tissue. The importance of dsDNA in lupus pathogenesis has been recognized for more than 50 years [33], and several approaches are now ongoing based on developing injectable agents that contain DNase that can either destroy the putative dsDNA-antibody immune complexes, or dissolve the NETS [56, 59-62]. On this basis,

the newly developed DNase formulations should be evaluated as possible therapies for APS, lupus, and AAV.

As already noted, in all three diseases immune complexes can activate complement, but the immune complexes can also interact with effector cells (monocytes, macrophages and neutrophils) that express Fc receptors, thus promoting inflammatory responses independent of complement [10, 48, 50]. There is a long history of the use of IVIG in the treatment of certain autoimmune diseases such as immune thrombocytopenia [63-65]. The mechanism of action of IVIG is still a matter of much debate, but it has been demonstrated to block Fc receptors and to inhibit complement activation by capturing nascent C3b. However, IVIG is expensive, heterogeneous, and impractical for long-term therapies. In terms of a next generation surrogate for IVIG, several groups of investigators have recently reported that recombinant multimers of the Fc region of IgG can work effectively as innocuous decoys to interact with Fc receptors on effector cells and thereby suppress the potential pathologic interaction of the cells with disease associated immune complexes [66-70]. Therefore these newly developed Fc multimers should be evaluated as possible therapies for APS, lupus, and AAV

Approaches that combine one or two additional targeting paradigms besides complement as a target are much more likely to be effective. These strategies can be tested in vitro in whole blood models developed by Mollnes and Lambris [71, 72] and later by Golay and Introna [73]. The key here is to include the additional orthogonal agents that have different targets. That is, e.g., combine a complement inhibitor with the next generation DNase formulation and/or an Fc multimer.

Whole blood, anticoagulated with citrate and or lepirudin, can be combined with autoantibodies from patient sera (anti-dsDNA, ANCA, APL) and the targeted antigens (e.g., dsDNA), or neutrophils. The readout will include consumption of complement, activation and disintegration of neutrophils and production of NETS. After the baseline for immune complex mediated pathologies is established, the experiments can be repeated in the presence of one or more of the inhibitors: anti-complement; formulated DNase; or Fc multimers.

These whole blood experiments can be extended further to ex-vivo experiments by adding the whole blood to endothelial cells in culture [74-78]. A variety of cells can be adhered to surfaces, and then exposed to the potential activating inflammatory agents. Extension of this approach would appear to be straight-forward. The key questions will focus on examining the action of immune complexes in injuring the adhered cells in whole blood, followed by tests of the potential inhibitor cocktails to prevent such damage. None of these experiments are easy, and they will require considerable efforts to optimize them. However, in view of the multiple factors, in addition to complement, that appear to be operating in APS, lupus and AAV, examination of these complex systems has the potential to lead to next generation therapies that could substantially enhance therapies based on only blocking complement.

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65. Hoffman

Brian Tumminello (ChemoCentryx):

CCXI Proposed Additional Questions for ANCA-Associated Vasculitis:

Since localized/limited disease is often associated with unrecognized systemic manifestations, are these terms relevant?

What parameters should be used and how do clinicians define complete remission in ANCA-associated vasculitis (i.e. preventing relapse/flares, improving renal function, improving QoL, preventing other end-organ damage, reduction/elimination of GC usage)? And how does this differ from a patient's perspective?

What other terminology besides remission should be utilized?

How is kidney recovery evaluated in ANCA-associated vasculitis?

Under what scenarios can persistent “grumbling” symptoms be considered active disease and when would this be considered severe?

How has the availability of new medications changed the current treatment paradigm with regards to remission?

What role does C5a/C5aR play in end-organ damage, specifically kidney damage?

Group 3: IC-MPGN, C3G and PIGN:

Suparna Mallik (Novartis):

Genetic Testing:

As noted earlier, we suggest adding points of discussion regarding the role of different pathways in each disease breakout. In this case, the CP and the AP in IC-MPGN. Perhaps prior to the genetic testing section, the following question can be asked: “What is the role of different complement pathways in IC-MPGN, C3G, PIGN?” Potentially probing on the roles of the pathways will add to the exchange in the subsequent sections on treatment.

Add:

4. Should family members be routinely screened for urinary abnormalities and kidney function among a subset of genetically-driven, diagnosed C3G patients?
5. How can we register the genetic data in a world-wide database, combined with disease outcomes and treatment?

Other Serological Tests

Add: What is the role for assessing CD68 and other markers of macrophase activity in glomerular tissue at the time of biopsy? Is inflammation in the kidney a marker for complement pathway activity?

Treatment of C3G, IC-MPGN, PIGN

12. Which is the current best approach to treatment of C3G and IC-MPGN? When should complement inhibition be considered?

13. What is the role of supportive care in treatment sequence? If supportive care is recommended, what is suggested the duration?

14. Can you differentiate on different types of complement inhibition? For example, is there a preference between proximal inhibition versus terminal inhibition? Additionally, for each disease, inhibition of which pathways and regulators would be recommended?

15. Should C3G and IC-MPGN be considered equivalent with respect to complement inhibiting therapies?

16. Which endpoints of response to treatment should be employed? *Please consider both a native kidney and transplanted kidney with disease recurrence when discussing.*

17. Which biomarkers, both serological, urinary and on the kidney biopsy, may be helpful in monitoring effectiveness of complement inhibition in C3G and IC- MPGN? *Which of these biomarkers are currently measurable in clinical practice today (specifically non-research grade assays)?*

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? *Can we expect differences in efficacy and safety outcomes with regards to central complement inhibition versus complement inhibition targeting a specific pathway?*

13. Is there a role for complement inhibition in PIGN?

Raja Ramachandran (Postgraduate Institute of Medical Education and Research, Chandigarh, India):

Breakout group 3:
Other serological tests: It may be worthwhile to add "How can we organize a standardization of anti-factor H, anti-factor B, and anti-C3b antibodies
in IC-MPGN, C3G, and PIGN".
Treatment of C3G, IC-MPGN, PIGN: Can we add "duration of therapy and endpoints for stopping treatment (especially in a responsive patient)"

Dima Decker (Apellis Pharmaceuticals, Inc.):

Thank you for the opportunity to provide comment on your posted scope for the KDIGO Controversies Conference on the Role of Complement in Kidney Disease. We would like to submit the following topics and questions below for consideration by the organization for Breakout Group 3.

- An addition of a section to this breakout group which discusses the challenges of and updates on the diagnosis and pathogenesis session for C3G and primary or idiopathic IC-MPGN
    - What similarities of pathogenesis should be considered for C3G and idiopathic or primary IC-MPGN?
    - What diagnostic tests should be considered to exclude proliferative glomerulonephritis with monoclonal immunoglobulin deposit (PGNMID)?

- Other serological tests section:
    - How important and how relevant are the measurement of AH50, CH50, C3a and C3b? Do they have significance when considering disease pathway identification and disease progression?
    - What is the potential role of biomarkers in monitoring for post-transplant recurrence?

- Treatment of C3G, IC-MPGN, PIGN section:
    - Question 10: consider clarifying primary or idiopathic IC-MPGN with respect to complement inhibiting therapies, if applicable.
    - Consider adding a topic on the role of prophylactic complement inhibition in the post-transplant setting
    - Are there any considerations for the pediatric population?

Group 4: IgAN, IgAV and MN:

Anuja Java (Washington University school of medicine in St. Louis, MO, USA):

I have a couple thoughts:
1) For FSGS, IgA and Lupus, it would be helpful to try and specify how to tease out the role of complement when TMA is associated with these conditions?

2) Under biomarkers, clarifying how urinary biomarkers for complement compare to blood and if they have a role in any of the diseases?

Suparna Mallik (Novartis):

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?

    c. In which proportion of patients is activation in the alternative pathway observed versus the lectin pathway?

    d. How can AP/LP activation be assessed over the courses of the disease (without biopsy)?

    e. Do we need to differentiate patients and adjust treatment accordingly in the future?

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? *What is the role for assessing CD68 and other markers of macrophase activity in glomerular tissue at the time of biopsy?*

5. Are there any (complement -associated) biomarkers that could determine the varying levels of complement activation at diagnosis and over the course of the disease?

6. Can we improve the use of the MEST-C scoring for guidance and treatment?

Raja Ramachandran (Postgraduate Institute of Medical Education and Research, Chandigarh, India):

Breakout Group 4:

MN treatment: Can we add: Impact of complement inhibition on antibody monitoring (PLA2R or others).

Group 5: Complement-Mediated Forms of HUS

Jakub Ruszkowski (Medical University of Gdańsk, Poland):

What is the optimal management of complement-mediated HUS in case of increasing CH50 during standard eculizumab therapy?

Len Woodward (aHUS alliance Global Action):

A very topical issue of concern to aHUS patients (in remission and or susceptible) is whether COVID 19 triggers aHUS or is an infection HUS like Stec-HUS, or both. The "etc" in item 11 of the Complement Mediated Forms of HUS list may bring it within scope, but, given the high profile of COVID and the recency of its controversy, if it is in scope then it should appear before "etc" to make it more visible. At a minimum a consensus on "more research needed" would be a welcome outcome.

Maria Vicenta Mireya Carratala Rios (association patient):

As a patient association we are interested in the issue of kidney transplantation in ahus patients with living relatives related to the same mutation. (Factor h, u others)

Marina Noris (ISTITUTO MARIO NEGRI IRCCS):

1) Breakout group 5: Complement-Mediated Forms of HUS.
pregnancy-associated HUS should be considered as a primary form.
I also suggest to add a bullet on: incomplete penetrance.

Suparna Mallik (Novartis):

Add:

12. *Should family members of those genetically-identified causes of aHUS be screened for urinary abnormalities and kidney function?*

Raja Ramachandran (Postgraduate Institute of Medical Education and Research, Chandigarh, India):

Breakout Group 5:
Can we add "Kidney Transplant in patient with HUS- monitoring and management"