Global Science. Local Change.

KDIGO Controversies Conference on Therapies Targeting B Cells in Immune-Mediated Kidney Diseases

June 26–29, 2025
Panama City, Panama

Scope of Work

Kidney Disease: Improving Global Outcomes (KDIGO) is an international organization whose mission is to improve the care and outcomes of people with kidney disease worldwide by promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines. KDIGO also regularly hosts Controversies Conferences on a focused subject pertaining to kidney disease to review state-of-the-art evidence, set priorities for improving patient care and outcomes, and highlight priority areas for research.

CONFERENCE BACKGROUND AND RELEVANCE

Glomerular diseases have traditionally been managed using a combination of approaches designed to modify lifestyle-associated kidney and cardiovascular risk factors, lower proteinuria, and globally suppress the immune system with systemic glucocorticoids and broad-spectrum immunosuppressive agents such as cyclophosphamide or mycophenolate mofetil (MMF). While the benefits of lifestyle modification (e.g., exercise, smoking cessation, healthy diet) and lowering of proteinuria (e.g., blood pressure control, inhibition of the renin-angiotensin system, salt restriction) are not usually associated with significant adverse events, the long-term use of high-dose glucocorticoids combined with immunosuppressive agents that target multiple arms of the immune system simultaneously exposes patients to significant risk for infection-associated morbidity and mortality, and is associated with metabolic, bone, and cardiovascular morbidity. The nephrology community has long recognized the need for more selective immunomodulatory approaches targeting specific pathomechanisms of individual glomerular diseases.[1-3]

Recently, important advances in our understanding of glomerular disease pathogenesis have led to an increased recognition of the role of B cells in several glomerular disorders, including IgA nephropathy (IgAN), lupus nephritis, membranous nephropathy, minimal change disease, focal segmental glomerulosclerosis, anti-glomerular basement membrane disease, and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis.[4-13] As a result, ongoing trials are now examining therapies that modulate or deplete B cells to arrest the immunopathogenesis of disease. Cell-based approaches such as infusion of CD19 chimeric antigen receptor (CAR) T cells have achieved deep B cell depletion, demonstrating sustained disease remission in a small series of patients with proliferative lupus nephritis[14, 15] as well as rescue from hemodialysis for one patient with rapidly progressive lupus nephritis.[16] Similarly, a T cell engager (i.e., a bispecific engineered antibody designed to bring T cells into contact with particular B cells for targeted depletion) has been used to successfully treat one patient with refractory lupus nephritis.[17]

Therapies that deplete or modify B cells present risks for patients with glomerular diseases, such as diminished immune responsiveness during infectious disease outbreaks. Further, initiation of deep B cell depletion with CAR T cells presently requires aggressive suppression of the immune system and may increase risk of malignancies. The challenges for physicians taking care of patients with autoimmune and immune-mediated glomerular diseases include how best to deploy B cell therapies and at what level of B cell depletion/modulation is needed for specific glomerular diseases and individuals.

CONFERENCE OVERVIEW

The objective of this KDIGO conference is to gather a global multidisciplinary panel of nephrologists, rheumatologists, pathologists, immunologists, and cell therapists to address the therapeutic strategy of targeting B cells for managing autoimmune and immune-mediated kidney diseases. The efficacy and safety of B cell–targeting approaches will be reviewed to assess how they supplement or replace existing management paradigms.

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. This highly interactive conference will invite key thought leaders and relevant stakeholders who will critically review the literature and our current state of understanding in this area and address the clinical issues outlined in the **Appendix: Scope of Coverage**. The conference output will include publication of a position statement to help guide KDIGO and others on therapeutic management of and future research on B cell–targeted therapies in kidney diseases.

APPENDIX: SCOPE OF COVERAGE

Issues that all breakout groups should consider during their discussions

- What is B cell depletion, what is deep B cell depletion, and how shall we define and measure these? Please consider peripheral versus tissue (e.g., lymph node) depletion and need for or use of biopsies in these definitions.
- The term "immune reset" is being used a lot lately. What does that mean?
- What endpoints should be sought when using cell therapies and T cell engagers given that these therapies present safety risks beyond what we usually consider with more conventional therapeutics? For example, consider the ideas of drug-free remission and relapses.
    - Even with more "conventional" B cell targeted therapy, what responses are we looking for?
- Safety concerns when using B cell depleting therapies (alone or with other immunomodulatory therapies), and consideration for chronic use as may be needed in some situations
    - Please include infection prevention, monitoring Ig levels, threshold for IVIG replacement, administration of vaccinations, fertility, and pregnancy considerations
- Is there a scientific rationale of preferring one B cell therapy approach over another (e.g., efficacy, safety, patient and physician preference, cost)? Are there situations when B cell therapy should not be first choice?
- How do we think about combining B cell therapies with other immunosuppressives or even with other B cell therapies? How do we think about sequencing B cell therapies? How do we think about withdrawing B cell therapies? How do we think about preventing relapse?
- Please consider children and adults in your discussions.

Issues to consider when formulating research agenda

- Understand the B cell subsets and autoantibody profiles and how they contribute to disease
- How do we begin to decide how to match patients with their needed depth of B cell depletion?
- Are there other areas of key unmet need?

Breakout Group 1: IgA Nephropathy (IgAN)

1. What is the ideal approach for managing IgAN with B cell therapies: B cell depletion (anti-CD19, anti-CD20), plasma cell depletion (anti-CD38), B cell modulation (anti-BAFF, anti-APRIL, anti-BAFF/APRIL), or combinations of these therapies? What about sequential versus continuous therapy, and what about an induction-maintenance concept? How to sequence drugs, and when to taper them? Consider potential differences between IgAN and IgAV.
2. In IgAN, is the preferred target galactose-deficient IgA1 (Gd-IgA1) or antibodies to Gd-IgA1 (IgG/IgA anti-Gd-IgA1), and how should the target dictate B cell therapeutic choice? Or rather assess total IgA in serum?
3. How do anti–B cell therapies compare with other available approaches in IgAN (e.g., Nefecon, systemic corticosteroids, complement inhibitors)? Should B cell therapies be combined with other IgAN therapies, and what combinations would be appropriate? What are the indications to start B cell therapies in IgAN?
4. What biomarkers or histological features are needed to appropriately guide B cell therapies in IgAN, including but not limited to circulating B cell levels, tissue B cell levels, B cell subsets, and/or B cell growth or maturation factors (e.g., APRIL/BAFF)?
5. Is there a role for very deep B cell depletion in IgAN (e.g., therapy with CAR T cells or T cell engagers)?
6. How do the efficacy and safety of B cell therapies for IgAN compare to the newly approved or soon-to-be approved therapies (e.g., targeted-release mucosal glucocorticoids, endothelin antagonists, and complement inhibitors)?

Breakout Group 2: Primary Membranous Nephropathy (MN)

1. What are the B cell therapies that have proven to be effective in MN (e.g., anti-CD20)? Is there also a role for plasma cell therapy (i.e., anti-CD38) and/or B cell modulation with APRIL/BAFF, BAFF, or CD40/CD40L inhibitors? Who should receive B cell therapy? How should one dose it (i.e., induction/maintenance/duration), and when and how should it be tapered?
2. Are B cell therapies single treatments for MN, or should they be combined with other immunosuppressive therapies?
3. Since anti-PLA2R antibodies have been considered a biomarker for MN, how should these and other MN autoantibodies be integrated into B cell management of MN? Are there additional biomarkers that should/could be considered when using B cell therapies, including but not limited to circulating B cell levels, tissue B cell levels, and B cell subsets? Does the approach to B cell therapies differ between patients who are anti-PLA2R-positive versus -negative (or with another antigen or unknown antigens)?
4. How do efficacy and safety of B cell therapies for MN compare to traditional immunosuppressive therapies (e.g., calcineurin inhibitors [CNI], cytotoxics)?
5. In patients treated with anti-CD20 who do not respond, how should therapy be approached?
6. Is there a role for very deep B cell depletion (e.g., CAR T, T cell engagers, CAAR NK) in MN?

Breakout Group 3: Podocytopathies

1. Which podocytopathies would be most amenable to B cell–directed therapy?
2. What is the role of B cell depletion (e.g., anti-CD19, anti-CD20), plasma cell depletion (anti-CD38), B cell modulation (anti-BAFF, anti-APRIL, anti-BAFF/APRIL), or combinations of thereof in the treatment of podocytopathies? Is there a role of targeting CD40?
3. How do anti–B cell therapies compare with other available approaches (e.g., steroids, CNI, MMF, cytotoxic therapy) for the treatment of podocytopathies with respect to safety and efficacy?
4. What biomarkers are needed to appropriately monitor B cell therapies in podocytopathies, including but not limited to circulating B cell levels, tissue B cell levels, B cell subsets, and antibodies?
    a. How could these strategies be used for patient monitoring from a safety and efficacy standpoint?
    b. How could they help in determining timing and dosing of patient retreatment?
5. Is there a role for very deep B cell depletion (e.g., CAR T or T cell engagers, bi-specific antibodies) in podocytopathies?
6. What are the differences between adults and children with podocytopathies in terms of their response to B cell modulating agents and in terms of the safety profile of these agents?
7. What are the risks of using B cell–modulating agents in treating immune-mediated podocytopathies? In what way and for how long should a patient with an immune-mediated podocytopathy be monitored after having received a B cell–modulating agent?

Breakout Group 4: Lupus Nephritis (LN), ANCA-Associated Vasculitis (AAV), and Other Systemic Diseases

1. As B cell therapies have proven to be effective in systemic diseases (e.g., anti-CD20, anti-BAFF, anti-CD38, anti-CD40, CAR T cell therapy), in which order and combination should B cell agents be commenced? Is it possible to recommend a hierarchical order of increasing B cell depletion therapies in systemic diseases dependent on disease subtype and severity (e.g., rituximab, obinutuzumab, belimumab, CAR T, extrarenal manifestations)? What are the disease-specific considerations?
2. The B cell therapies used in systemic diseases provide varying degrees of B cell depletion, both circulating and in tissue. What biomarkers or histological features are already in use, and which are needed to monitor degree of depletion, efficacy and safety?
3. How do efficacy and safety of B cell therapies for systemic diseases compare to other disease-modifying agents (e.g., MMF, cyclophosphamide)?
4. What precautions (e.g., vaccinations) should be exercised and in which vulnerable populations (e.g., preexisting malignancy) during B cell therapy administration?
5. How should B cell therapies be combined with other available immunosuppressants/immunomodulatory therapies for systemic diseases?
6. When should one consider avoiding or discontinuing B cell therapy in systemic diseases?
7. The aim is restoring immune tolerance. Is a cure realistic with cell-based therapies and if so, should cell therapy be offered to patients only after failing other therapies or at time of disease diagnosis?

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