IgA nephropathy: "State of the art": a report from the 15th International Symposium on IgA Nephropathy celebrating the 50th anniversary of its first description

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On September 27–29, 2018, the International Symposium on IgA Nephropathy, organized by the International IgA Nephropathy Network, was held in Buenos Aires, Argentina, celebrating the 50th anniversary of the first description of IgA nephropathy by Berger and Hinglais in 1968. The meeting was attended by over 200 scientists and clinicians from 26 different countries across the globe. We report some key insights drawn from the meeting–including the molecular pathogenesis, genetics, pathology, and therapeutics of IgA nephropathy.

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The 15th International Symposium on IgA Nephropathy (IgAN), organized by the International IgAN Network in Buenos Aires, Argentina, hosted over 200 scientists and clinicians from 26 nations on 6 continents, including many young scientists as well as seasoned investigators. The symposium coincided with the 50th anniversary of the first description of IgAN by Berger (Figure 1)[1] and Hinglais. Just 2 years had passed since the last meeting organized by the International IgAN Network in Tours, France; however, it was encouraging to see the breadth and depth of new data that had been generated over this time. Topics ranged from molecular immunology, population genetics, and structural biology to clinical risk stratification and novel therapeutic strategies. Cognizant of the emerging new therapies that are leading to a surge in interest in IgAN from pharmaceutical companies, 1 session covered clinical trial design, the regulatory process for drug approval, and the impact of the Kidney Health Initiative. The symposium closed with a look to the future and included new information on risk stratification and the establishment of global registries to foster collaboration and generate new knowledge.

The symposium opened with a reminder of some of the characteristics that enabled Berger to make the first description of IgAN: his open-mindedness (he thought IgA should be studied in glomerular disease, whereas current thinking at the time was dominated by findings in animal models that focused on IgG deposition being responsible for initiating immune glomerular injury); his interest in making clinicopathological correlations; and his recognition of the value of collaboration (which led him to obtain the only "clean" anti-IgA reagent available at the time).[2]

An overriding theme of the symposium was the already close working relationships of research groups from across the globe, exemplified by the work to generate and validate the Oxford Classification of the pathology of IgAN, and a soon to be published IgAN risk calculator. Such a highly collaborative environment will undoubtedly lead to greater insight into the complex and heterogeneous entity we call IgAN.

Another recurring theme of the meeting was that we still have no proof that IgAN is a single disease or that it is the same disease in different parts of the world; this is an

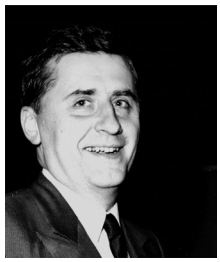

Figure 1 | Jean Berger. Reprinted, with permission, from Feehally J, Levy M, Monteiro R. Jean Berger (1930–2011). *Kidney Int.* 2011;80:437–438.[1]

insightful perspective that impacts our approach to studying its pathogenesis, assessing prevalence and risk of progression, as well as responses to therapy.

Genomics and IgAN

Although a genetic contribution to pathogenesis has been appreciated for decades, no genetic risk factors for IgAN were convincingly identified until the era of genome-wide association studies (GWAS). GWAS is particularly suitable for approaching complex multifactorial diseases such as IgAN. The GWAS studies have only been performed in patients who presented with clinical manifestations and had a renal biopsy identifying IgAN. Those with mesangial IgA deposition, but no clinical manifestations have not been included, nor has phenotyping been sufficient to investigate possible genetic associations with risk of progressive IgAN. In IgAN, GWAS loci discovered to date explain approximately 8% of overall disease risk. A population gradient in these risk alleles matches the known ethnic and geographic differences in susceptibility to IgAN with a clear West-to-East prevalence gradient, the disease being most common in East Asia, less common in Europe, and probably rare in Africa (though data from that continent are sparse).[3] Moreover, the distribution of GWAS risk alleles has been correlated with local pathogen diversity, especially for helminthic species, suggesting the multilocus adaptation to endemic pathogens as a potential evolutionary mechanism that has shaped the present-day epidemiology of IgAN. Additional evidence for the role of host-pathogen interactions in the genetic susceptibility to IgAN comes from the observation that most known GWAS-risk loci encode genes involved in the maintenance of the intestinal epithelial barrier or participate in the direct response to mucosal pathogens or both. These loci highlight several pathways as central to the pathogenesis, including antigen processing and presentation (*MHC* region), the complement system (*CFHR1/3* and *ITGAM-ITGAX* loci), regulation of mucosal IgA production (*TNFSF13* and *LIF/OSM* loci), and innate immunity against pathogens (*DEFA, CARD9, ITGAM-ITGAX,* and *VAV3* loci).[4] Systematic gene enrichment analyses point specifically to the "Intestinal Immune Network for IgA Production" as being among the key pathogenic pathways, providing several molecular targets for potential therapeutic intervention. GWAS have also highlighted the important role of the alternative complement pathway in IgAN, which is regulated by factor H and the competitive factor H antagonists, such as factor H–related protein 1 (encoded by *CFHR1*). Individuals who inherit a common deletion of *CFHR1* and *CFHR3* (*CFHR3,1Δ*) have lower concentrations of factor H–related protein 1 (FHR1), and thus are protected from overactivation of the complement pathway in IgAN.[4]

Pathogenesis

Given the continuing uncertainty that IgAN is a single entity, glomerular IgA deposition may be a final common endpoint for a number of pathogenic pathways, each subject to different regulators and initiators. Accepting these limitations, a number of key abnormalities now identified in IgAN are likely to contribute to pathogenesis.[3,5]

The synthesis of IgA1 with some *O*-glycans deficient in galactose (Gd-IgA1) appears to be increased and these glycoforms of IgA1 are present in circulation at increased levels.[5,6] Gd-IgA1 is autoantigenic, and circulating IgG autoantibodies are induced, resulting in the formation of pathogenic IgA1-containing circulating immune complexes, some of which deposit in the glomeruli and induce renal injury.[3,5] Mesangial deposition of circulating Gd-IgA1 may also result from direct binding to mesangial cells or matrix. Upstream factors determining synthesis of Gd-IgA1 are likely to involve an abnormal mucosal immune response, driven by either dysregulated immune regulation within the mucosal-associated lymphoid tissue (MALT) or dysbiosis of the normal mucosal microbiota. It is probable that genetic factors contribute variably to many elements of this paradigm, although their relative contribution is likely to vary from patient to patient and population to population.[3,5]

New work presented at the symposium supports a role for Gd-IgA1–IgG immune complexes in the pathogenesis of IgAN. Engineered immune complexes using a Gd-IgA1 myeloma protein mimicking Gd-IgA1 in IgAN and a recombinant Gd-IgA1-specific IgG autoantibody derived from a patient with IgAN are capable of inducing similar protein-tyrosine kinase phosphorylation and proliferative responses in cultured primary human mesangial cells.

Mucosal infections may be associated with episodes of visible hematuria and an increase in circulating IgA immune complex levels in IgAN.[3,5] Systemic IgA responses to mucosal antigen challenge are exaggerated in IgAN and many of the features of mesangial IgA are those typically associated with IgA produced in the mucosal lymphoid tissue. Mucosal IgA, unlike systemic IgA, is typically polymeric, of low affinity, and relatively poorly *O*-galactosylated, the physicochemical characteristics typically observed in serum and glomeruli in IgAN.[3,7] Furthermore, GWAS in IgAN have identified susceptibility loci in genes that are directly associated with intestinal mucosal immunity.[4]

Proteomics and glycomics remain in their relative infancy with respect to understanding IgAN. Mass spectrometry–based glycoprofiling of the IgA1 hinge region has been technically challenging but is now providing important insights in the heterogeneity of the IgA1 hinge region in health and

disease and over the next few years is likely to redefine the nephritogenic IgA1 *O*-glycoforms responsible for IgA deposition and triggering of glomerular injury in IgAN.[8]

There is growing interest across biomedicine in the role of the microbiome both in health and disease. The gut microbiome exerts a direct regulatory effect on the MALT, and this involves ligation of pattern recognition receptors on both intestinal epithelial cells and MALT immune cells, including dendritic cells and lymphocytes, in particular T helper cell 17 and regulatory T cells.[9,10] A number of murine models have been developed that illustrate this complex interaction among gut microbiota, the MALT, and development of mesangial IgA deposition including the BAFFtg, ddY, and α1KI-CD89Tg mice.[11] In the latter mouse model, expressing human IgA1 and CD89, antibiotics were able to reverse mesangial IgA1 deposits. What is also apparent from these models and studies of other mucosal sites, including the tonsils, is that the B-cell activation factor of the tumor necrosis factor family (BAFF)–a proliferation-inducing ligand (APRIL) axis of B-cell regulation, which is critical to IgA class switching and plasma cell survival in the MALT, is dysregulated in IgAN and can be directly influenced by gut microbiota through Toll-like receptor ligation on mucosal dendritic cells.[12] These are provocative observations, but it is important to recognize that the murine IgA system differs substantially from the human system, and to date, there is still no mouse model that shows IgA1 mesangial deposition directly leading to chronic kidney disease and renal failure. Activation of primary mesangial cells by these complexes could be inhibited by the protein-tyrosine kinase inhibitor dasatinib, providing further proof-of-concept data for the use of protein-tyrosine kinase inhibitors in IgAN.[7]

Toll-like receptor ligation has been shown not only to drive polyclonal, T-cell independent, IgA class switching and IgA synthesis in the MALT but also to modulate post-transcriptional modification of the IgA1 protein by directly down-regulating the synthesis of glycosyltransferase transcripts and *O*-glycosylation of mucosal IgA.[13] Much more work is required to better understand the complex relationship between the microbiota and IgA synthesis by the MALT in IgAN and whether interference with the gut microbiome might be a therapeutic avenue in IgAN. It must also be noted that early clinical studies on the microbiome in IgAN have not always assessed confounders, such as the effect of chronic kidney disease *per se*, diet, ethnicity, and geographical area, and often failed to include high numbers of control subjects with disease.

The Oxford Classification of IgAN

The Oxford (initially based on the MEST score, defined by the presence [1] or absence [0] of M: mesangial proliferation; E: endothelial proliferation; S, glomerular sclerosis; T, tubular atrophy and interstitial fibrosis) Classification of IgAN has been validated many times since its first description in 2009 and was updated in 2017 with the addition of the C score for presence of crescents in the biopsy. One new approach now requiring systematic evaluation is the addition to routine biopsy evaluation of CD68 staining for identification of glomerular macrophages to better delineate the E (endothelial hypercellularity) lesion.[14] There was also discussion of subdivision of the S (segmental sclerosis) lesion to distinguish sclerosis due to previous segmental inflammation from true podocytopathy.[15] IgAN has been regarded as an exemplar of mesangial injury, but it is now being appreciated that there may be podocyte injury in IgAN, consistent with experimental work that shows that stress on mesangial cells can have direct effects on podocyte behavior. The peripheral out-pocketings of the glomerular basement membrane form a continuous channel system that is open to the mesangium and contains the capillaries. The mechanical stability of this system is largely maintained by the mesangial cells, which insert along the paramesangial aspect of the glomerular basement membrane. In conditions of increased mesangial area, as may occur in IgAN, a lengthening of the mesangial axis is followed by the prolapse of the capillary and associated podocyte detachment with loss into the urinary space.[16] Podocyturia and podocyte-specific molecules shed into the urine may yet prove valuable tools for pathophysiologic investigations in IgAN, but such studies have suffered from lack of standardization, cellular instability, and lack of suitable podocyte markers.[17,18]

Debate also continues over the importance of vascular lesions in IgAN, in particular those associated with endothelial injury and thrombotic microangiopathy.[19,20] The reported fraction of IgAN patients with morphologic lesions of thrombotic microangiopathy varies greatly from 2% to 50%. These differences could be due to the morphologic criteria used to define such lesions. One study reported thrombotic microangiopathy lesions in >50% of biopsies with IgAN, which may be explained by the employment of fuchsinophilic staining in affected vessels on the Masson trichrome stain, the lack of electron microscopy assessment, and also the fact that CD61 stain was performed in only a few cases.[19,20] These vascular lesions are reportedly more common in Asians and quite rare in Caucasians. However, the findings reported to date agree that the presence of thrombotic microangiopathy in IgAN is associated with severe hypertension, as well as more severe renal impairment and proteinuria, which are all features associated with worse clinical outcomes in IgAN. A multicenter study to determine whether the addition of a thrombotic microangiopathy-vascular score to the current Oxford MEST-C score is warranted.[19] Finally, it was also recognized that the Oxford classification should be tested for validity in both IgAN recurrence following kidney transplantation and in IgA vasculitis (IgAV).[19]

Complement

The GWAS findings that various alleles controlling complement pathway proteins are associated with both disease risk and protection from disease in IgAN, along with improved techniques to detect these proteins in both fluid phase and in tissue are leading to new evidence on the contribution of complement to renal injury in IgAN. Circulating complement FHR5 may predict progression of IgAN, and novel data presented at the symposium associated glomerular FHR5 deposition with risk of progression in IgAN. These findings require further evaluation as risk predictors useful in clinical practice.[21]

Risk stratification

A major goal of the International IgAN Network's research strategy has been to develop an accurate and validated risk stratification tool that would allow clinicians to predict accurately and easily future risk of renal function decline in their patients following diagnosis with a kidney biopsy. The new International IgAN Network risk prediction model comes from an unprecedented international research collaboration that has enabled pooling of data from over 3000 IgAN cases from Europe, North and South Americas, and East Asia with consistent longitudinal phenotyping as well as biopsy scoring.[22] This has generated the first validated clinicopathological prediction tool in IgAN, valid in multiple ethnic groups, that uses histologic and clinical predictor variables that are readily available at the time of kidney biopsy (extent of proteinuria, presence of hypertension, estimated glomerular filtration rate [eGFR], MEST-C biopsy score) to calculate the 5-year risk of a 50% fall in eGFR, development of end-stage renal disease, or death. This prediction model represents important progress in the development of accurate clinically personalized risk stratification in IgAN. An accurate risk prediction tool will also allow more reliable recruitment of higher-risk patients, thus increasing power and improving the feasibility and cost of clinical trials in IgAN.[22]

Biomarkers

Reliable biomarkers are desirable for the noninvasive diagnosis of IgAN and to more fully delineate the risk for progression. From the data presented it was clear that no biomarkers (tested alone or in panels) yet replace a renal biopsy, as a diagnostic and prognostic test, nor add to the information available when combining the biopsy findings with conventional clinical parameters including proteinuria, blood pressure, and eGFR.[23,24]

A number of putative IgAN-specific biomarkers were discussed, including serum levels of Gd-IgA1, Gd-IgA1–specific autoantibodies, and IgA-IgG immune complexes; urinary Gd-IgA1, CD89, CD71, and podocyte urokinase-type plasminogen activator receptor.[18,25–27]

Each of these biomarkers now needs to be evaluated in the new risk prediction model that provides a study platform to see whether they add value in predicting risk and guiding clinical decision making in IgAN.

IgAN in children

Further high-quality studies are still needed in children with IgAN to better delineate natural history, clinicopathological risk factors for progression, and optimal treatment pathways. The Oxford Classification has already been validated in children, but the long-term predictive value of clinical data may be less relevant in children than in adults due to the greater potential for remission in children. In children who present at an early age, with a fast rate of progression, an underlying genetic cause must be considered.[28]

IgA vasculitis

IgAV (formerly known as Henoch-Schönlein nephritis) remains less studied than IgAN. Little is known about the pathogenic processes that drive the extrarenal manifestations (most commonly in skin and gut) that are pathognomonic of this rare form of vasculitis, and the relationship between IgAN and IgAV is still debated although many regard them as part of a spectrum rather than as 2 distinct entities. A new initiative of the International IgAN Network is to validate the Oxford Classification in IgAV, and to address this, a global collaborative of pediatric and adult nephrologists and pathologists has assembled a cohort of over 1000 renal biopsies in IgAV correlated with clinical outcome, which is now being evaluated.[29]

Treatment

Supportive care remains the basis for management of IgAN, regardless of the level of proteinuria, stage of chronic kidney disease, or histopathologic findings. Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, adequate blood pressure control, a low-sodium intake diet, aerobic physical exercise, adequate loss of weight, and tobacco avoidance are the basis for effective management of IgAN.[30]

At the symposium there were planned debates on the relative merits of corticosteroids, mycophenolate mofetil, and tonsillectomy in the treatment of IgAN. Opinions were polarized but the discussions emphasized the continuing lack of high-quality trials' evidence to support treatment recommendations for all patients with IgAN. An individualized approach when talking to patients about treatment options still remains opinion-based. Corticosteroids may have an antiproteinuric effect, particularly in the setting of extensive glomerular inflammation; however, the Supportive versus Immunosuppressive Therapy for the Treatment of Progressive IgAN (STOP-IgAN) and Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING)-I studies clearly documented the potential for serious side effects of corticosteroids, making it essential that the risks and benefits of corticosteroids are discussed with each patient.[31–35]

The STOP-IgAN trial randomized patients to supportive treatment or to steroids alone or in conjunction with sequential cyclophosphamide and azathioprine based on the eGFR. Immunosuppression transiently reduced proteinuria over 3 years but had no impact on kidney function and only resulted in significant, particularly, infectious adverse events. Proteinuria reduction occurred mostly in the steroid group and not in the immunosuppressive combination therapy group. Optimized supportive treatment was associated with a very slow loss of kidney function in the control group, so that the study was underpowered to detect eGFR-based outcomes. In the TESTING-I trial, in which high-steroid doses were employed, a beneficial effect on proteinuria and eGFR was demonstrated, but the study was stopped prematurely mainly due to infections. Noteworthy, no pneumocystis pneumonia prophylaxis was given to immunosuppressed patients either in the STOP-IgAN or TESTING-I studies. The impact of

lower doses of steroids and routine pneumocystis pneumonia prophylaxis is now being studied in TESTING-II (results expected in 2020).

Treatment of pediatric IgAN is more poorly evidence-based than for adults; pediatric nephrologists commonly adopt a tailored approach to treating pediatric cases at high risk of progression, often involving corticosteroids.[28]

Based on limited data from China, an argument was made that mycophenolate mofetil could be used as a corticosteroid-sparing agent, but it was agreed there are no data to support the use of mycophenolate mofetil in Caucasians with IgAN.[36,37]

There remains a small amount of prospective controlled randomized clinical trial (RCT) data to support the use of tonsillectomy in IgAN. However, observational, uncontrolled cohort studies suggest efficacy of tonsillectomy with pulsed corticosteroids in Japan.[38] A Japanese RCT compared tonsillectomy with steroids versus steroids alone and found some benefit in proteinuria reduction in the tonsillectomy group but no impact on eGFR over 12 months.[39] However only one-half of the patients received renin-angiotensin system blockade, there was no long-term follow-up to evaluate changes in eGFR, and the study was underpowered to assess any impact on risk of end-stage renal disease. There remains a dearth of data on tonsillectomy in Caucasians.[40] Further data from RCTs are ideally needed to resolve the debate over the value of tonsillectomy in IgAN, but there seems little prospect that such trials will be undertaken.

Although many clinicians are beginning to use the Oxford MEST-C score as a guide to therapy (most notably in regarding the E lesion as an indication for immunosuppression), this approach remains unproven. More prospective data is required before the scoring system can be verified as a useful tool in selection of treatment modality. It is for example not known whether MEST-C score may change after a period of supportive care and, if so, how this should influence a decision to use imunosuppression.

Clinical trials now underway are typically collecting renal biopsy scores alongside clinical data so more information may be forthcoming, but the ideal (although demanding) approach will be to develop trials that use MEST-C elements as part of the selection criteria, in order to test definitively the value of the MEST-C score in therapeutic decision making.[41]

A summary of the 2017 Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference on Glomerular Diseases was recently published in *Kidney International*.[30] It has been agreed that KDIGO guidelines on the management of IgAN and IgAV would be updated and will be a valuable resource as we await the outcomes of a number of trials now underway.

Forthcoming therapies

Over the past few years, there has been unprecedented interest in new therapeutic approaches for IgAN. A number of novel agents are being evaluated including some phase 2 and 3 trials.[42,43] An important facilitator for this growing interest has been the development of strategies to shorten RCTs by avoiding reliance on end-stage renal disease as a required endpoint for regulatory approval.[44] The report from the Kidney Health Initiative Surrogate Endpoints for Clinical Trials in IgA Nephropathy project was published recently.[45] The overarching principles and outcomes of the project were discussed ahead of formal publication of the work later this year. The practical implications of using an early change in proteinuria as a clinical trial endpoint and how this may be used in a drug approval pathway were discussed.[44] It was repeatedly stressed that these welcome changes will only impact on future management of IgAN if nephrologists become even more effective in recruiting their patients to the various clinical trials now open.

One area of interest is the therapeutic modulation of the mucosal immune system.[46] Thus, therapeutic strategies aimed at suppressing the mucosal lymphoid tissue, the site of mucosal B-cell induction, may provide an alternative to traditional regimens of systemic immunosuppression and specifically target nephritogenic IgA production in IgAN and with lower systemic side effects. Steroid delivery to the terminal ileum using a targeted-release formulation of budesonide was effective in a phase 2 RCT and is now being evaluated in a phase 3 trial.[42,47] Other strategies focused on modulation of mucosal B-cell programming include hydroxychloroquine (Toll-like receptor antagonism); antagonism of BAFF-APRIL signaling (belimumab, blisibimod, and atacicept).[47]

Another area of significant potential in IgAN is complement inhibition. Both the lectin and the alternative pathways play important roles in determining the degree of glomerular inflammation that occurs in response to mesangial IgA deposition.[3,21] Pharmacologic interventions to both complement pathways are currently being evaluated in IgAN.

Tyrosine kinase inhibitors (already used in cancer therapy) may have a place in treatment for in kidney disease. Spleen tyrosine kinase has important roles in mediating immune responses and effector inflammatory processes and is downstream of activating domains of B-cell receptors and Fc receptors.[48] An international multicenter phase 2 clinical trial has investigated the efficacy and safety of the spleen tyrosine kinase inhibitor fostamatinib in IgAN patients with optimized control of hypertension and proteinuria with angiotensin-converting enzyme inhibitor or angiotensin II–receptor blocker for 90 days before randomization. The patients then were randomized to groups receiving fostamatinib 100 mg twice daily, 150 mg twice daily, or placebo for 24 weeks. Although the full analysis remains unpublished, an early press release indicates the trial did not achieve statistical significance for its primary endpoint, mean change in proteinuria, although prespecified subgroup analysis showed a greater but nonsignificant reduction in proteinuria with fostamatinib.[49]

For the future

To conclude the meeting, there was a vibrant discussion on how we answer the key unanswered questions in IgAN and IgAV over the next few years. A critical step is our ability as an IgAN research community to access large cohorts of

well-characterized patients. This was achieved for the development of the Risk Assessment Tool, although the large cohort only had clinical and renal biopsy data available and mean follow-up was only 5 years.[22] Now prospectively collected, large, multiethnic patient cohorts are needed with deep phenotyping and well-characterized and uniformly collected biorepositories of renal biopsy tissue, blood, urine, and DNA. The international IgAN community is developing such global resources—for example the Strategy for Patient-Oriented Research in Glomerulonephritis (SPOR-GN) cohort in Canada, the Research on Adverse Drug Events and Reports (RaDaR) IgAN and IgAV cohorts in the United Kingdom, and the international Research on Adverse Drug Events and Reports (iRaDaR) cohorts in South and East Asia. Each are beginning to collect clinical data and tissue to an agreed protocol and there is an open collaborative consensus that these repositories will be accessible for collaborative research, and they are linked to other relevant resources for study of glomerular disease, such as Cure Glomerulonephropathy (CureGN) in North America.[50]

The International IgAN Network is galvanized and collegial, and we are optimistic that there will be much new to learn at the next symposium in September 2021 in Prague.

DISCLOSURE

HT is a member of the Advisory Board for Calliditas and Novartis. JB is a member of the Advisory Boards for Novartis, Omeros, Calliditas, Rigel, Retrophin, and EMD Serono. The other authors declared no competing interests.

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