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Half a century of IgA nephropathy: achievements, frustrations and challenges

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Abstract. *IgA nephropathy is the most common glomerulonephritis worldwide. This disease has a tremendous economic impact because renal replacement therapy is expensive and hard-to-reach. It also represents a social problem because children and young adults in their second and third decades of life are affected by the IgA nephropathy, and it is the most active period of human life with highest work productivity. Many retrospective studies have shown that 40% of biopsy-proven IgA nephropathy patients develop end-stage kidney disease in 20 years after their biopsy disease.*

The biomarker research in IgA nephropathy has experienced a major splash in recent years with great number of scientific reports. Individual biomarkers often lack sensitivity and specificity with impairment of disease specificity as a consequence. The review describes a novel approach based on a panel of biomarkers for pathogenic process of IgA nephropathy. Integration of genetic, clinical, and bioinformatics data sets could optimize the specific value of each biomarker in a multimarker panel. This is a inspirational and promising approach for precision medicine and personalized therapy in IgA nephropathy.

Half a century into the original description of IgA nephropathy, there is still no specific therapy for this condition Although the scarcity in treatment advances could be related to the disease's complex pathogenesis. The evolution of different therapeutic approaches is reviewed over time and resulted in the 2012 Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for Glomerulonephritis that presently is being updated, and provide collation of recent data on various forms of immunosuppressive agents. Existing approaches to treatment of IgA nephropathy are described with focus primarily on innovative therapeutic strategies currently being evaluated in IgA nephropathy that were not discussed in the 2012 Kidney Disease Improving Global Outcomes Clinical Practice Guidelines.

Keywords: *IgA nephropathy, biomarkers, immune system, proteinuria, gut, therapeutic approach.*

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Півсторіччя IgA нефропатії: досягнення, розчарування та проблеми

ТОВ "GlaxoSmithKline Pharmaceuticals в Україні"

Резюме. *IgA-нефропатія є найпоширенішим гломерулонефритом у всьому світі. На IgA-нефропатію в основному страждають діти та молоді люди працездатного віку, що призводить до необхідності високовартісних витрат на лікування нирковою замісною терапією та інвалідизації у молодому віці. Адже ретроспективними дослідженнями продемонстровано, що 40% пацієнтів з морфологічно підтвердженою IgA-нефропатією досягають термінальної стадії хронічної хвороби нирок через 20 років після біопсії.*

Дослідженню біомаркерів IgA-нефропатії присвячена значна кількість наукових публікацій. Огляд присвячений новим підходам у діагностиці та лікуванні, заснованим на панелі біомаркерів IgA-нефропатії. Інтеграція генетичних, клінічних та біоінформативних даних може оптимізувати діагностичну цінність кожного біомаркера.

Після першого опису IgA-нефропатії пройшло півсторіччя, але до цих пір не існує однозначного підходу до лікування. Еволюція різних терапевтичних підходів щодо лікування гломерулонефриту переглядалась з плином часу та підсумована у рекомендаціях Kidney Disease: Improving Global Outcomes «Clinical Practice Guideline for Glomerulonephritis» (2012), які зараз оновлюються. Представлені підходи до лікування IgA-нефропатії не обговорювались у рекомендаціях 2012 року та описані у фокусі інноваційних терапевтичних стратегій, що потребують подальшої оцінки.

Ключові слова: *IgA нефропатія, біомаркери, імунна система, протеїнурія, кишечник, терапевтичний підхід.*

Epidemiology. IgA nephropathy (IgAN) is the most common glomerulonephritis worldwide. This disease has a tremendous economic impact because renal replacement therapy is expensive and hard-to-reach. It also represents a social problem because children and young adults in their second and third decades of life are affected by the IgAN, and it is the most active period of human life with highest work productivity. Many retrospective studies have shown that 40% of biopsy-proven IgAN patients develop end-stage kidney disease (ESKD) in 20 years after their biopsy disease [1]. This is a period of life during which people are very active and have high work productivity [2].

IgA nephropathy (IgAN), or Berger's disease, was described in 1968 [3]. This common kidney disease characterized by persistent microscopic hematuria and/or mild proteinuria and/or recurrent episodes of gross hematuria in concomitance of upper respiratory tract infections. IgAN is diagnosed by the presence of diffuse mesangial IgA deposits, especially the subset of IgA1 in glomeruli.

IgA nephropathy (IgAN), or Berger's disease, is the most common primary glomerular disease worldwide, but varies largely in its geographic distribution. The systematic review of the frequency of IgAN in the five continental areas of the world arose from a need to determine the worldwide burden of this disease, which remains the most common cause of ESKD among children with permanent urinary abnormalities and young adult patients with biopsy-proven primary glomerular disease [1]. IgAN is more frequent in Asian populations (for example, 45 cases per million population/y in Japan) than in Caucasians (for example, 31 cases per million population/y in France) [4].

These differences are owing to some relevant aspects: (1) systematic mass screening of urine in populations is performed in Asia, but not in Western countries; (2) general practitioners and health care professionals in Western countries underestimate persistent microscopic hematuria and/or mild proteinuria in apparently healthy individuals causing late referral to a nephrologist; and (3) different indications for kidney biopsy in individuals with persistent urinary abnormalities are different in many countries. Frequency of IgAN observed in a nephrology center with a high incidence of kidney biopsies is higher than in a regional renal biopsy registry. If biopsy indications will not be so tight and screening will be used widely, if early therapy will follow it, the global burden of end-stage kidney disease caused by IgAN will be decreased [4].

Pathogenesis. Downstream pathogenetic events leading to tubulointerstitial damage in IgAN are characterized by mesangial-podocytic-tubular cross-talk pathways, in which mesangial deposition of polymeric IgA1 and IgA1-containing immune complexes leads to a podocytopathy that promotes subsequent tubular cell dysfunction to further podocytic injury [5]. Scientific evidence suggest that specific inflammatory pathways play important pathogenetic roles in IgAN, such as complement-mediated and spleen tyrosine kinase–driven intrarenal inflammation.

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As soon as hematuria concomitant with pharyngitis is a constant feature in IgAN, participation of the mucosal immune system was considered to be the main pathogenetic factor. Recent observations have confirmed hyper-reactivity of gut-associated lymphoid tissues in IgAN patients [6]. As mentioned below, the emerging concepts on the interaction between the host and the gut microbiota, and a gut-renal connection in IgAN are discussed now [7].

Recently, the Japanese Renal Biopsy Registry reported that among approximately 20,000 native renal biopsies performed in the year 2010, 30% of biopsy specimens were diagnosed with IgAN. Thus, approximately 6,000 incident IgAN patients were diagnosed in the country. Moreover, the investigators reported that 68% of cases had CKD stage 1 or 2 [8].

Data from many countries [2, 4] have shown that these young patients may have three different clinical courses, as follows: (1) short or long remission of the disease (absence of urinary abnormalities) in a low number of individuals (2%-5%); (2) slowly progressive renal deterioration over a 20-year period after the kidney biopsy in a variable percentage of subjects; or (3) rapid deterioration in a few cases (5%-10% of patients). Early biopsy would promote early diagnosis and therapy, which may reduce the progression of renal damage [9].

Some guidelines for healthcare professionals for the diagnostic screening of IgAN: 1) in the presence of asymptomatic urinary signs such as persistent microscopic hematuria and/or mild proteinuria, the general practitioner should not underestimate the symptoms and must refer the patient to a nephrologist. 2) nephrologists could include the clinical pattern of persistent microscopic hematuria and/or mild proteinuria in the indications for a kidney biopsy 3) children and adolescents should at least be included in these as well as individuals in the military service or employment, even though there are pros and cons to mandatory urinalysis screening.

Dynamic development of histologic classification of IgA nephropathy. Since its description in 1968, a number of histologic descriptions and classification systems have emerged. In 1967, Antoine et al presented immunofluorescence patterns in renal lesions, among which he identified a group of patients with chronic glomerulonephritis or with purpuric lesions whose biopsy specimens showed glomerular deposits of IgA. In 1968, Berger and Hinglais described 25 patients with recurrent hematuria and mesangial IgA deposits that surmounted IgG deposits [3]. The eponym of Berger's disease was introduced in 1973, and by 1975 the defining features of IgA nephropathy were consolidated [9].

In 1997, Haas published a new histologic classification based on his observations of 244 patients with IgAN [10] . The Haas study aimed to establish relevant clinicopathologic correlations and to identify potential histopathologic markers of outcome [10]. The schema recognized FSGS-like lesions as part of the spectrum of IgAN. Five classes were described. A comparison between the Lee and Haas classes is presented in the table 1.

Table 1

Lee [11] and Haas [10] Classification Systems (cited without cjanges from [12])

Grade	Lee	Haas
I	Mostly normal glomeruli	Minimal histologic lesion
II	<50% of glomeruli with mesangial hypercellularity and sclerosis Rare small crescents	Focal segmental glomerulosclerosis
III	Diffuse mesangial proliferation Occasional adhesions and small crescents	Proliferative glomerulonephritis in ≤50% of glomeruli Crescents might be present
IV	Diffuse marked mesangial proliferation ≤45% of glomeruli with crescents Frequent segmental and global sclerosis	Proliferative glomerulonephritis in >50% of glomeruli Crescents might be present
V	Severe mesangial proliferation >45% of glomeruli with crescents Frequent segmental and global sclerosis	≥40% glomerular sclerosis and/or tubular atrophy

The Oxford Classification of IgAN pioneered the use of an evidence-based approach to histologic classification.Four histologic variables were found to be both reproducible and independently associated with clinical outcome: mesangial hypercellularity (M0, ≤50% glomeruli; M1, >50% of glomeruli showing mesangial hypercellularity); endocapillary hypercellularity (E0, absent; E1, present); segmental glomerulosclerosis (S0, absent; S1, present); and tubular atrophy/interstitial fibrosis (T0, absent or involving ≤25% of the cortex; T1, 26%-50% of the cortex; T2, >50% of the cortex). M, S, and T scores were found to be independent predictors of either rate of loss of renal function or renal survival in the entire cohort, using a multivariate analysis that included initial eGFR and proteinuria, and follow-up MAP and proteinuria. The E score was considered as independent predictor of outcome in patients who did not receive steroid/immunosuppressive therapy. These scores include the MEST score [13, 14].

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The prognostic value of the MEST criteria has been validated in adults and children by more than 20 studies, including more than 7 000 Asian, European, and North American patients [15]. T score is consistently the strongest predictor of clinical outcome in these validation studies; T1/2 represents advanced chronic damage and late-stage disease at the time of diagnosis and therefore a shorter time to end stage. The Validation of the Oxford Classification of IgA Nephropathy (VALIGA) study was a large validation study that included 1 147 IgAN patients from 13 European countries [15]. Its broad inclusion criteria allowed extrapolation of the Oxford Classification criteria to patients who were not addressed in the original Oxford Classification study, that is, patients with minimal proteinuria (<0.5 g/d) or decreased renal function at presentation (eGFR < 30 mL/min). Patients with low initial proteinuria showed less frequent MEST lesions, and had 90% 5-year renal survival. In this subgroup, the presence of M1 and/or E1 predicted progression to higher levels of proteinuria (>1 and 2 g/d). Patients with a low eGFR were significantly older, presented with greater initial proteinuria (2.4 g/24 h), showed more frequent M1, S1, and T1-2 lesions, and had an average renal survival of 50% at 5 years [15].

It must be emphasized that, as is the case for most clinicopathologic studies of IgAN, the Oxford Classification study was retrospective and uncontrolled for treatment. The VALIGA study confirmed the prognostic values of mesangial hypercellularity (M1 lesions), including in patients with low initial proteinuria and in pediatric IgAN; among the 174 children included in the VALIGA study cohort, M1 was associated with lower renal survival and increasing proteinuria, and to be the strongest predictor of eGFR slope. Similarly to endocapillary lesions and crescents, the predictive value of mesangial hypercellularity was attenuated by immunosuppression, indicating that M1 lesions are possibly steroid-responsive, especially in children [15].

The Oxford Classification of IgAN now includes 5 variables, Mesangial hypercellularity, Endocapillary hypercellularity, Segmental Sclerosis, Tubular atrophy/interstitial fibrosis, and Crescents (MEST)-C [14] (table 2).

Table 2

2016 Oxford Classification of IgAN [14]

Variable	Definition	Score	
M	Mesangial hypercellularity	M0	Absent to ≤50% of glomeruli
		M1	>50% of glomeruli
E	Endocapillary hypercellularity	E0	Absent
		E1	Present
S	Segmental sclerosis/adhesions/synechiae	S0	Absent
		S1	Present
T	Tubular atrophy and interstitial fibrosis	T0	Absent to ≤25% of the cortex
		T1	25%-50% of the cortex
		T2	>50% of the cortex
C	Crescents	C0	Absent
		C1	1%-24% of the glomeruli
		C2	≥25% of glomeruli

The Prognostic Modeling Working Group's aim is to optimize outcome prediction for individual patients by developing a risk prediction model that incorporates histologic, clinical, and other data. An initial study [12, 15] including more than 900 patients from three different cohorts (Oxford Classification, North American, and VALIGA), showed that a model based on a combination of MEST criteria and initial clinical data performed as well as 2-year clinical data in predicting the risk of reaching a combined end point of ESRD or 50% loss of eGFR. This earlier risk prediction was independent of treatment with renin-angiotensin system blockade or immunosuppression. This was a large and detailed IgAN data set and will enable risk stratification according to ethnicity in both adults and children. The ultimate goal is to develop web-based and mobile application calculators that may be used in the management of individual.

One of the central aims of the Oxford Classification study and the IgANN/RPS working groups is to identify histologic lesions that are responsive to immunosuppression and thus use the biopsy in guiding therapeutic decisions. There is evidence from several of the large retrospective studies described earlier that endocapillary hypercellularity and crescents (E1 and C1/2) are associated with more rapid loss of renal function in the absence of immunosuppression, and patients with these lesions have a better outcome if treated with steroids. The confirmatory evidence from prospective randomized clinical trials (RCTs) is needed for clarification of the role of histology in guiding therapy.

The scoring of histologic lesions that comprise the MEST-C criteria were found to be highly reproducible in the original Oxford Classification study which aim was to resolve differences in the evaluation of challenging lesions [14]. Interobserver variation in the interpretation of glomerular and other lesions in the renal biopsy specimen may be improved by providing clear lesion definitions and illustrated guidance. An RPS Working Group currently is developing consensus definitions that can be applied to any glomerular disease, not just IgAN.

Studies over the past decade have identified those histologic lesions that are associated with progressive IgAN in the absence of immunosuppression, and shown which lesions are treatment-responsive. In the near future, methods for assessing renal biopsy specimens will be refined, accurate prediction models that incorporate clinical and histologic data will be developed, and the role of the renal biopsy in guiding standard therapy and the use of new therapeutic agents will be determined [16].

Mesangial-podocytic-tubular cross-talk and its leading role in IgAN.

A subgroup of IgAN with proximal tubular epithelial cells (PTECs) and tubulointerstitial damage often is associated with rapid progression to end-stage renal failure. Human mesangial cell–derived mediators lead to podocyte and tubulointerstitial injury via mesangial-podocytic-tubular cross-talk. Podocytes are the final gatekeeper of the glomerular filtration barrier. This barrier has three major components: the fenestrated endothelial cell, the glomerular basement membrane (GBM), and the podocyte with their slit diaphragms. Foot processes (FPs) of podocytes contain an actin-based cytoskeleton that is linked to the GBM. FPs of podocyte form a highly branched interdigitating network with the FPs of neighboring podocytes. Slit diaphragm bridges the filtration slits between opposing podocyte FPs, forming the final barrier to urinary protein loss [5].

The most distinctive structural change in injured podocytes is cell hypertrophy or sclerosis. Podocyte hypertrophy or sclerosis at the tubular pole (tip lesion) is associated with heavy proteinuria at presentation of IgAN and a more rapid decrease in renal function. Segmental sclerotic lesions commonly are seen in glomeruli in IgAN. In the Oxford Classification, the presence of segmental sclerosis was found to predict an adverse outcome. It was suggested that the sclerotic lesions seen in IgAN form mainly as a consequence of healing of previous inflammatory lesions [5].

Deposition of IgA-IC to human mesangial cells (HMCs) triggers the production of tumor necrosis factor-α (TNF-α) and TGF-β, and down-regulates the expression of nephrin, ezrin and other proteins of the slit diaphragm by podocytes. Mesangial-derived TNF-α up-regulates the TNF-α receptor-1 (TNFR1) expression by podocytes and increases the podocytic TNF-α synthesis. Up-regulated TNF-α acts on the TNFR1 and increases podocytic interleukin (IL)-6 release. Furthermore, TNF-α up-regulates the expression of podocytic TNF-α receptor and angiotensin II receptor 1 (AT1R) through a nuclear factor κ light-chain enhancer of activated B cells (NF-κB)-dependent mechanism. This TNF-α/TNFR1/AT1R axis modulates further nephrin reduction and apoptosis in podocytes [17].

Podocytopathy in IgAN may be accompanied by tubulointerstitial changes including tubular atrophy, interstitial infiltrates, inflammation, and fibrosis. Proteinuria is a surrogate marker of tubulointerstitial injury [5, 17].

The mechanism for the formation of IgA-IC is highly variable in different patient groups as a result of the following: (1) marked differences in the extent of serum IgA1 O-glycosylation and the hinge-region–specific autoantibodies (2) the presence or absence of additional components in the process of immune complex formation (usually these components include soluble CD89 of different molecular weight, complements, and antigliadin antibodies); (3) the variation in the size of IgA-IC and light chain composition of the IgA1. It is likely that both genetic and environmental factors play contributory roles in the process of IgA-IC formation. IgA-IC binds to mesangial cells but not podocytes or tubular epithelial cells. Mesangial deposition of IgA-IC leads to the activation of HMCs, leading to mesangial cell proliferation, matrix expansion, and the release of proinflammatory and profibrotic mediators. Mesangial deposition of IgA immune complexes induced glomerulopodocytic cross-talk through the release of TNF-α, TGF-β, complement components, and other bioactive factors [5].

Gut-associated immune system and IgAN. The relationship between IgA nephropathy (IgAN) and the mucosal immune system has been considered since the identification of this renal entity by [3] 50 years ago. IgA, which is predominant in the mesangial deposits of IgAN, is produced mostly by the mucosal-associated lymphoid tissue (MALT) and is the most represented immunoglobulin in mucosae [18]. The clinical hallmark of IgAN is the manifestation of gross hematuria, often coincident with an upper respiratory-tract infection, hence most of the interest has been focused on the oropharyngeal and tonsillar-associated lymphoid tissue

in the past, however, some associations between IgAN and intestinal disorders were reported decades ago [19]. In some patients the mucosal infection triggering hematuria involves the intestine, with acute diarrhea, or in patients with Crohn's disease it involves the ileocecal region. Patients with celiac disease and inflammatory bowel diseases have an increased frequency of IgAN, indicating a connection stronger than sheer chance [20]. Recent data have suggested investigators reconsider old theories of a role of dysregulated GALT in which the genetic conditioning, the gut dysbiosis, and the reaction to diet components may play a combined role in the development and progression of IgAN. This hypothesis led to a search for innovative treatment approaches to IgAN focused on corticosteroids specifically targeting GALT in the Peyer's patches and possible dietary components and intestinal microbiota modulations [8].

Gluten-free diet for two periods of 1 and 6 months was associated with a significant reduction in IgA-IC, followed by a rebound after intervals of 1 and 3 months of a gluten-containing diet. These fluctuations of IgA-IC were not observed during diets avoiding other alimentary components, such as meat or eggs. After 6 months on a gluten-free diet, all patients had normal IgA-IC levels. Gluten-free diet may have interrupted the self-maintaining circle of gluten-dependent abnormal intestinal permeability [18].

Patients with IgAN, either children or adults, have increased intestinal permeability, tested by the 51Cr-EDTA method often found to be associated with an increased level of IgA directed against alimentary antigens, suggesting exposure to immunogenic alimentary antigens and breakdown of oral tolerance [18]. Several studies have focused on investigated signs of intestinal mucosal inflammation, particularly on features typical of celiac disease in patients with IgAN. In patients with IgAN, duodenal inflammation of varying degrees has been detected, with a high presence of small-bowel T cells and increased expression of HLA-DR and GroEL stress protein and mucosal cyclooxygenase [21].

The involvement of GALT in IgAN suggests the possible benefits of drugs targeted to the mucosal B lymphocytes in Peyer's patches, which are supposed to be primed to produce Gd-IgA1, the initial step in the pathogenesis of IgAN. Decreased production of Gd-IgA1 would reduce the consequent autoantibody formation, and macromolecular IgA1 circulation and renal deposition. To this aim, a new formulation of the glucocorticosteroid budesonide was designed with a targeted-release formulation to release the active drug in the distal ileum, where Peyer's patches mostly are represented. Results from a phase 2b trial indicated that targeted-release formulation budesonide has the potential to become the first IgAN-specific treatment targeting intestinal mucosal immunity upstream of disease manifestation [21].

There are several old and new data indicating a role for gut-renal connection in IgAN, based on genetic, microbial, and dietary factors, which interact in inducing functional modifications of the intestinal mucosal immune system, favoring the development of IgAN. This pathogenetic mechanism opens an interesting new perspective in developing and testing new approaches on a large number of patients based on the use of drugs targeting GALT as well as a gluten-free diet and microbiota manipulations [18, 21].

Biomarkers and Precision Medicine in IgA Nephropathy. In 2011 the hypothese appeared that the pathogenesis of IgAN was based on four hits. These hits are as follows: 1) the occurrence of an abnormal IgA1 glycosylation process leading to galactose-deficient IgA1 (Gd-IgA1); 2) the formation of antiglycan antibodies against Gd-IgA1; 3) the formation of nephrogenic circulating immune complexes; and, 4) the deposition of these complexes in the mesangium of glomeruli leading to renal injury with variable clinical expressions (macrohematuria, microscopic hematuria, acute renal failure, and chronic renal damage). This four-hit hypothesis is supported by high levels of aberrant glycosylated IgA1 and circulating immune complexes in the blood of patients with IgAN, and by the in vitro proliferation of human mesangial cells and the secretion of extracellular matrix proteins in the presence of immune complexes of IgAN patients [22].

High serum levels of Gd-IgA1 may be considered a diagnostic biomarker of the disease, and their persistence is predictive of renal function decline. Therefore, this biomarker also may be prognostic, but its validation in large multiracial cohorts of IgAN patients with long-term follow-up evaluation is necessary [22].

Recent systematic review [22] analyzed 22 eligible studies that evaluated the serum levels of Gd-IgA1 in IgAN patients, individuals with other glomerulonephritis, and controls. The meta-analysis provided evidence that adults and children with IgAN had high serum levels of Gd-IgA1, thus showing that this biomarker may be considered a useful indicator for the diagnosis of IgAN. However, in the present meta-analysis no significant correlation with the severity of the disease was found. Therefore, the investigators concluded that this biomarker may be specific for the suspected diagnosis of IgAN in individuals with permanent urinary abnormalities who refuse renal biopsy, mainly in family members of IgAN patients. However, it cannot be considered a sensitive biomarker for evaluating disease severity.

Circulating let-7b and miR-148b may be considered a reliable and noninvasive clinical biomarker to predict the probability of having IgAN. The use of this combined biomarker may be considered as a first approach for the diagnosis of IgAN in family members of IgAN patients who have permanent urinary abnormalities, such as microscopic hematuria and/or mild proteinuria and who are in apparently good health, or individuals with an overt clinical picture of suspected IgAN who refuse renal biopsy [22].

The presence of an increased fraction of Gd-IgA1 in the blood of IgAN patients stimulates the immune

system to produce IgG and IgA antibodies because the truncated IgA1 hinge region is recognized as nonself. Therefore, the measurement of circulating IgA1-IgG or IgA1-IgA immune complexes in the blood may be considered another diagnostic parameter for monitoring the clinical course of the disease [2].

The IgA receptor family is composed of six receptors, but myeloid IgA fragment crystallizable alpha receptor or CD89 specifically binds IgA and might contribute to the formation of serum polymeric IgA. Soluble CD89 (sCD89) receptors are present in the blood and sCD89-IgA complexes have been measured in IgAN patients. Stable high levels of circulating sCD89-IgA immune complexes have been detected in IgAN patients without disease progression, whereas low levels were found in patients with severe renal damage. The investigators speculated that sCD89-IgA immune complexes are more suitable to precipitate at the renal level and, consequently, are less represented in the peripheral blood, that`s why this biomarker may be taken into consideration for disease progression.

Podocyte depletion, which causes glomerular sclerosis and the persistent loss of podocytes in urine, is a proved marker of disease progression [2].

The classic process for the development of a diagnostic biomarker is based on three steps: discovery, validation, and confirmation. A biomarker should be independent of the disease outcome. In this case, the logistic regression analysis (univariate and multivariate) should show that the biomarker does not diminish in value in the presence of clinical factors. Thus, this approach determines the influence of other variables (demographic and clinical parameters) that reduce the biomarker's performance as a predictor of a disease [2].

However, the validation and confirmation of results in other cohorts of IgAN patients are few. Recently, clinical bioinformatics has been proposed to optimize the development of disease-specific biomarkers because it integrates clinical and laboratory findings, omics data, and bioinformatics [2]. The simultaneous evaluation of clinical and basic research data could optimize the specific value of biomarkers. A biomarker may be prognostic because it predicts the clinical outcome in the absence of therapy (natural story of the disease) or in the presence of a standardized therapy. On the other hand, a biomarker may be predictive when it is able to predict the benefit or lack of benefit in the presence of an established therapy.

The process for translating the biomarker from research to clinical practice is based on six steps: (1) research plan; (2) management of data; (3) engagement, education, and collaboration of patients including diverse populations; (4) innovation by designing a clinical trial; (5) evidence generated by the clinical study; and (6) translation in clinical practice [23]. Conventional medical practice is based on the standard of care obtained through the averaging of responses across large clinical trials. Precision medicine, which takes into account omics data, lifestyle, and environmental factors, is a new model tailoring medical treatment to the individual characteristics of each patient. Precision medicine can use big data, thus improving prevention, diagnosis, and therapy [23].

The first step of precision medicine in nephrology has been the genome-wide association studies that have compared gene mutations present in a large cohort of IgAN patients with numerous healthy controls. Another approach for precision medicine in IgAN is the molecular phenotyping of kidney biopsy specimens used for disease diagnosis [2].

Renal biopsy still remains the gold standard for clinical diagnosis in IgAN, but histopathology can demonstrate different biomarkers involved into pathogenesis of IgA nephropathy. The development of biomarkers will introduce molecular stratification of renal lesions and address precision medicine. Moreover, the systems pharmacology applied to the renal signatures may provide additional information on the use of old and new drug molecules that have as their target the discovered biomarker(s) [2, 23].

Therapy – adopted and novel appoach. Although IgAN was described 50 years ago this year, in 2018 there is no approved drug treatment for this disease. In 2016 the Kidney Health Initiative established a workgroup focused on Identifying Surrogate End Points for Clinical Trials in IgA Nephropathy. This workgroup is expected to publish a guideline on drug development in IgAN in 2018 that will recommend clinical trial end points that should be incorporated in all future IgAN clinical trials, making it more feasible for companies to invest in the research necessary to improve treatments for patients with IgAN [24].

Patients with minor urine abnormalities and normal blood pressure and glomerular filtration rate usually require only periodic monitoring. For other patients with proteinuria, a commonly adopted nonspecific approach is blockade of the renin-angiotensin system. Evidence accumulated from 56 studies among 2 838 participants showed that only antihypertensive drugs (mostly angiotensin-converting enzyme inhibitor (ACEI) or angiotensin-receptor blocker (ARB)) provided useful intervention, mainly by reducing proteinuria. In a meta-analysis of 585 patients from 11 randomized clinical trials (RCTs) significant renoprotection and reduction of proteinuria were achieved with an ACEI or ARB versus control [24].

Effectiveness of fish oil as a monotherapy is not proved. A European trial of 30 patients suggested that a RAS blocker combined with polyunsaturated fatty acids reduced proteinuria more than a RAS blocker alone [24].

A meta-analysis of seven nonrandomized studies (mostly from Japan) comprising 858 patients demonstrated that tonsillectomy combined with either standard or pulse corticosteroid treatment, but not tonsillectomy or corticosteroid treatment alone, resulted in higher remission rates with a favorable long-term outcome. Meta-analysis of 14 studies (also mostly from Ja-

pan) found positive effects of tonsillectomy plus pulse or conventional steroids. Outside of Japan, the benefits of tonsillectomy have not been documented [8, 25].

The KDIGO guidelines suggest that patients with persistent proteinuria greater than 1 g/d, despite 3 to 6 months of optimized supportive care (including ACEIs or ARBs and blood pressure control), and a GFR greater than 50 mL/min/1.73 m^2, receive a 6-month course of corticosteroid therapy [26].

Barratt et al. (2018) suggest not treating with corticosteroids combined with cyclophosphamide or azathioprine in IgAN patients (unless there is crescentic IgAN with rapidly deteriorating kidney function) and not to use mycophenolate mofetil (MMF) in IgAN [24].

KDIGO recommended that an RCT comparing MMF and corticosteroids versus corticosteroids alone in patients receiving optimal antihypertensive and antiproteinuric therapy should be performed, as well as an RCT to investigate the different efficacy of MMF in Asians versus Caucasians, including evaluation of drug and metabolite levels [26, 27].

In multicenter, open-label, randomized, controlled STOP-IgAN trial, immunosuppressive therapy added to comprehensive supportive therapy was compared with comprehensive supportive therapy alone. It was shown that the increase in full clinical remissions was driven exclusively by the glucocorticoid monotherapy arm, which produced a transient reduction in proteinuria in patients with relatively well-preserved GFR. The number of adverse events and GFR dynamics were more common in both immunosuppression arms when compared with supportive care [28].

The TESTING study was a multicenter, double-blind, randomized, clinical trial designed to evaluate the efficacy and safety of corticosteroids in patients with IgAN and proteinuria greater than 1 g/d and eGFR of 20 to 120 mL/min after at least 3 months of blood pressure control with RAS blockade. Patients were randomized 1:1 to oral methylprednisolone (0.6-0.8 mg/kg/d; maximum, 48 mg/d; n = 136) or matching placebo (n = 126) for 2 months, with subsequent weaning over 4 to 6 months. The primary renal outcome had occurred in 8 participants in the methylprednisolone group versus 20 in the placebo group, consistent with a potential renal benefit of oral methylprednisolone use in IgAN, although definitive conclusions could not be made because of early termination of the trial [13].

Both studies showed a reduction in proteinuria with corticosteroids, albeit a transient reduction in STOP-IgAN, however, renoprotection was seen only in the TESTING study, albeit on an interim analysis with a shorter follow-up period than was available in STOP-IgAN. There were limitations to both studies, principal among these were that neither study used renal biopsy features when determining patient eligibility and the follow-up time for both studies was relatively short for a disease that typically is slowly progressive. Differences in the proportion of patients with scarring lesions (Oxford S and T) versus proliferative lesions (Oxford M, E, and C) between the two studies and between the treatment arms within each study conceivably could have altered the response to immunosuppressant therapy, as shown in a recent clinical trial of MMF and prednisolone incorporating repeat renal biopsies. This is particularly important because proliferative lesions are seen more frequently in renal biopsy series from Asia than in series from Europe, and TESTING participants were almost exclusively Chinese whereas STOP-IgAN recruits were white Europeans. Until that time, corticosteroids should be used on an individualized basis, not dictated purely by eGFR and UPCR values, with involvement of the patient in the decision after an open discussion covering both the potential benefits and definite risks of taking corticosteroids for IgAN. [7, 13, 17, 29].

Two new RCTs of MMF in IgAN have been published since the 2012 KDIGO guidelines. The first of these was a US-based, double-blind, placebo-controlled RCT evaluating the efficacy of MMF in children, adolescents, and adults who had a UPCR of 0.6 g/g or greater (in males) and 0.8 g/g or greater (in females) after optimization on lisinopril (or losartan) plus a highly purified omega-3 fatty acid. The trial was terminated early at the recommendation of the Data Monitoring Committee because of the lack of benefit [27].

The second prospective, multicenter, randomized, controlled, open-label, 12-month study comparing MMF with prednisolone against prednisolone alone for the treatment of incident (biopsy within 1 month of enrollment) IgAN with active proliferative lesions (cellular and fibrocellular crescents, endocapillary hypercellularity, or necrosis), proteinuria of 1.0 g/24 h or greater, and eGFR greater than 30 mL/min [27]. Eligible patients received either MMF 1.5 g/d for 6 months, and prednisone 0.4 to 0.6 mg/kg/d for 2 months, and then tapered by 20% per month for the next 4 months, or prednisone 0.8 to 1.0 mg/kg/d for 2 months, and then tapered by 20% per month for the next 4 months. There was no significant difference in CR rates at 6 and 12 months, however, steroid-related adverse events were lower in the MMF group than in the prednisone group, and there was no difference in the total adverse event rates between the MMF and prednisone groups at 12 months. Endocapillary hypercellularity, crescents, and necrosis lesions in glomeruli had improved or disappeared after immunosuppressive therapy, however, in the MMF group there was a significant increase in global glomerular sclerosis that was not seen in the prednisolone group [27].

The US study of MMF monotherapy was consistent with other studies of MMF in predominantly Caucasian populations and supports the 2012 KDIGO advice not to use MMF in IgAN. Most of the supportive evidence for efficacy of MMF in IgAN has in factcome from Asia. This study from China should be commended for basing inclusion on renal biopsy features and per-

forming repeat renal biopsies, one of the few studies to do this in IgAN. Until the results of the TESTING Low Dose Study are available it would not be unreasonable to suggest that in Chinese patients being considered for corticosteroid therapy physicians should consider a steroid-sparing regimen including MMF (at the dose used in this study) as an alternative to reduce the risk of adverse events [17, 27, 29].

There is increasing evidence supporting a pivotal role of the mucosal immune system in the pathogenesis of IgAN. IgA nephropathy has been associated with diseases in which mucosal immune responses are abnormal, such as celiac disease and inflammatory bowel disease. Many of the features of mesangial IgA are those typically associated with IgA produced in the mucosal-associated lymphoid tissue (MALT). Two events thought to be critical are antigen-driven activation of the innate immune response, in particular through ligation of Toll-like receptors (TLRs), and B-cell activating factor (BAFF) and a proliferation inducing ligand (APRIL) signaling, pathways that now both are amenable to therapeutic manipulation [24]. Recent genome-wide association studies in IgAN that have identified susceptibility loci in genes that are associated directly with intestinal mucosal immunity [24]. Tonsillectomy removes a portion of mucosal tissue enriched with immunocompetent lymphoid cells, which are a significant source of secretory IgA. Although the long-term clinical benefit of tonsillectomy is controversial [24].

Hydroxychloroquine, a drug commonly used in systemic lupus erythematosus, is a potent inhibitor of TLR-9 and, to a lesser extent, TLR-7 and TLR-8, and inhibits antigen processing and presentation via alkalinization of proteasomes [24]. A recently published case-control study from China reported a significant reduction in proteinuria in patients treated for 24 weeks with 200 mg twice daily of hydroxychloroquine compared with those who received RAS blockade alone. In an open-label, uncontrolled, proof-of-concept, pilot study, the potential treatment effects and safety profile of Nefecon, a modified release formulation of budesonide specifically designed to deliver budesonide to the ileocecal Peyer's patches with minimal systemic exposure and side effects, were examined. Treatment with Nefecon 8 mg/d for 6 months resulted in a 23% reduction in urinary albumin excretion and a minor reduction in serum creatinine level and a modest increase of the GFR. No major corticosteroid-related side effects were reported [30].

The Effect of Nefecon in Patients With Primary IgA Nephropathy at Risk of Developing End-stage Renal Disease trial, a double-blind, randomized, placebo-controlled, phase 2b trial of Nefecon in IgAN that was reported in 2017 [30]. In this study 150 patients with persistent proteinuria greater than 0,75 g/d despite optimized RAS blockade were randomized 1:1:1 to receive 16 mg/d Nefecon, 8 mg/d Nefecon, or placebo, stratified by baseline UPCR. At 9 months, the mean UPCR had decreased by 27,3% in 48 patients who received 16 mg/d and by 21,5% in the 51 patients who received 8 mg/d; 50 patients who received placebo had an increase in mean UPCR of 2.7% [30]. The effect was sustained throughout the follow-up evaluation and the incidence of adverse events was similar in all groups, although 25 of 99 (25%) patients in the Nefecon groups discontinued treatment or follow-up evaluation, 16 because of adverse events. Systemic corticosteroid-related effects were among the most common adverse events, suggesting in the minds of some investigators that some of the administered budesonide (or one of its metabolites) may have acted systemically, rather than locally, to decrease proteinuria.

Clinical trials with blisibimod, atacicept, bortesomib and fostamatinib (a selective oral Syk inhibitor) are ongoing [24, 31], Rituximab showed no effectiveness in IgA nephropathy [32].

Recent genome-wide association studies have provided additional evidence to support a role for complement activation in IgAN. Given the evidence for complement activation in IgAN and the emerging availability of agents that selectively block complement activation, investigators are beginning to explore the utility of complement inhibition in IgAN [24].

Eculizumab, a recombinant, fully humanized, monoclonal antibody against complement C5, prevents cleavage of C5 and formation of both the membrane attack complex and the anaphylatoxin C5a. and is currently is approved for the treatment of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome [31]. There have been two case reports of eculizumab use in rapidly progressive IgAN. In both cases, eculizumab was associated with temporary benefit in stabilizing renal function or proteinuria, but in both cases, there was significant disease progression once eculizumab was discontinued. These case reports raised the possibility of complement inhibition as a treatment strategy in IgAN [31].

Avacopan, also known as CCX168, is an orally active, selective, and potent C5aR inhibitor that has been proven to inhibit C5a-mediated migration in in vitro and ex vivo chemotaxis assays. The clinical effectiveness of avacopan was shown in a phase II clinical trial in anti–neutrophil cytoplasmic antibody–associated renal vasculitis, administration of avacopan (+cyclophosphamide) was as efficacious as or more efficacious than the standard treatment (high-dose prednisolone + cyclophosphamide) [24]. A small proof-of-concept study also was performed in IgAN. After an 8-week run-in period on a maximum tolerated dose of a renin-angiotensin-aldosterone system inhibitor, patients started avacopan dosing, 30 mg twice daily for 12 weeks, with a 12-week follow-up period. Seven patients received avacopan treatment, and all 7 patients completed the study. At the end of 12 weeks, proteinuria was reduced in 6 of 7 patients, with 3 of the 7 patients showing significant improvement to a UPCR less than 1 g/g. At the end of the 12-week period after treatment, the UPCR in 2 of these 3 patients returned to baseline levels, while the improvement was maintained in the third patient. Avacopan appeared to be safe and well tolerated [24].

OMS721 is a fully human monoclonal antibody targeting MASP-2 that currently is being evaluated for the treatment of thrombotic microangiopathies and complement-associated renal diseases, including IgAN. Initial results from a phase IIa study (Safety Study of IgAN, lupus nephritis, membranous nephropathy, and C3 Glomerulopathy Including Dense Deposit Disease Treated With OMS721) have been presented at both the European Renal Association–European Dialysis and Transplant Association Congress and American Society of Nephrology meeting in 2017, and suggest that OMS721, and inhibition of the lectin pathway, significantly reduces proteinuria in IgAN [**24, 33**]. Further data are awaited.

With an improved understanding of the genetic and immunologic basis for IgAN, alongside a changing regulatory environment, we are now observing an increasing number of exploratory studies of novel therapies in IgAN. It is hoped that over the next decade some of these new therapies will evolve into approved treatments for IgAN, and lead to the clearer understanding of the role of established immunosuppressants such as corticosteroids and MMF and ultimately nephrologists will be able to offer a rational approach to the treatment of this common glomerulonephritis.

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