FRONTIER

Update on immunoglobulin a nephropathy. Part Ⅱ: Clinical, diagnostic and therapeutical aspects

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Abstract

Immunoglobulin A nephropathy (IgAN) is characterized by different clinical manifestations and by long-term different outcomes. Major problem for the physicians is to understanding which patients are at risk of a disease evolution and to prescribe the right therapy to the right patients. Indeed, in addition to patients with a stable disease with no trend to evolution or even with a spontaneous recovery, patients with an active disease and patients with a rapidly evolving glomerulonephritis are described. Several histopathological, biological and clinical markers have been described and are currently used to a better understanding of patients at risk, to suggest the right therapy and to monitor the therapy effect and the IgAN evolution over time. The clinical markers are the most reliable and allow to divide the IgAN patients into three categories: The low risk patients, the intermediate risk patients and the high risk patients. Accordingly, the therapeutic measures range from no therapy with the only need of repeated controls, to supportive therapy eventually associated with low dose immunosuppression, to immunosuppressive treatment in the attempt to avoid the evolution to end stage renal disease. However the current evidence about the different therapies is still matter of discussion. New drugs are in the pipeline and are described. They are object of randomized controlled trials, but studies with a number of patients adequately powered and with a long follow up are needed to evaluate efficacy and safety of these new drugs.

Key words: IgA nephropathy prevention and control; IgA nephropathy; IgA nephropathy diagnosis; IgA nephropathy prognosis; IgA nephropathy classification; IgA nephropathy therapy

Core tip: Primary immunoglobulin A nephropathy (IgAN) is the most frequent glomerulonephritis. The IgAN is a relatively benign disease however, the long term prognosis should not be considered mild, because, after

20 years of disease evolution, 25% of the patients are going into chronic renal failure. It is essential to find out the risk factors predicting the evolution to end-stage renal disease (ESRD) and to select those patients who may benefit from immunosuppressive treatment. For all patients, it is essential to have a regular clinical control to check any disease evolution, in order to avoid or delay the disease progression to ESRD.

INTRODUCTION

Previously[1] we highlighted that, the diagnosis of immunoglobulin A nephropathy (IgAN) is principally based on a renal biopsy because there are different histological image results and different clinical presentation.

As the clinical presentations may be extremely different a tentative clinical classification aimed for the best therapy may be particularly useful.

Floege *et al*[2] categorized the clinical scenarios of IgAN into four classes: (1) patients diagnosed accidentally while looking for clinical manifestations such as reduced glomerular filtration rate (GFR), hypertension and urinary abnormalities. Such patients may be affected by IgAN and are called the silent majority; (2) patients affected by recurrent macroscopic hematuria strictly connected with acute infective diseases occurring in the upper respiratory tract. Such patients are also called typical IgAN patients and, in addition to hematuria, may be affected by proteinuria, hypertension and reduced GFR, which represent signs of disease evolution[3]; (3) patients presenting atypical signs such as nephritic syndrome and acute or rapidly progressive renal disease; and (4) patients with IgAN recurrence after kidney transplantation.

In addition to these categories, there are patients presenting acute kidney injury (AKI) accompanying macroscopic hematuria, due to acute tubular necrosis and intratubular erythrocyte casts. The relevance of this IgAN presentation is represented by the good prognosis not characterized by a disease progression.

Finally, IgAN may affect subjects who are otherwise healthy as documented by biopsies of kidneys suitable for transplantation or by autopsies of subjects not affected by renal diseases[4,5].

A further difficulty in decision making on therapeutic approaches is related to the fact that most subjects with IgAN may have a benign course or even disease resolution as documented by cohorts of patients followed for 10 years after diagnosis in China and Spain[6,7].

Such extremely variable clinical presentations and disease evolution have two principal consequences: (1)

most guidelines concerning IgAN, such as the Kidney Disease Improving Global Outcomes (KDIGO)[8], are based on a low level of evidence and are often based on opinions. As a consequence, there are few guidelines based on recommendations and the majority are only suggestions. Indeed, whether to treat and the beneficial effects of many treatments remain to be better validated[9]; and (2) There is a need for research on histological, biological and clinical markers that are able to predict the risk of IgAN progression and to guide therapeutic decisions and monitor therapeutic results.

Indeed, only a fraction of IgAN patients require treatment to prevent disease progression, and predicting which patients are at risk of progression is of overwhelming importance. Different histological, biological and clinical markers of prognosis have been identified, and other markers will likely be validated[10].

RESEARCH METHODOLOGY

We have analyzed the available papers on IgAN diagnosis, IgAN prognosis and IgAN therapy by a review of the currently available papers. A literature search was performed using PubMed (NCBI/NIH) with the search words "IgAN diagnosis", "IgAN prognosis", "IgAN biomarkers", "IgAN classification", and IgAN therapy". As first line research the papers published in the last three years were examined. Paper selection has been mede according the relevance of the journal, the authors, the dimension of the study and the novelty of the findings. So doing 40 papers recently published have been selected, then we proceeded in a backward way and studies previously published have also been included. Studies currently under way were searched for in "clinical trial.gov" and the European EUDRACT register. As clinical trial.gov also includes studies that to date are either closed or have not started, we selected only randomized controlled trials (RCTs) that are active and enrolling patients. So doing we report 15 RCTs out of the 68 that may be found on clinical.trial.gov. The RCTs exluded are either terminated or closed or not enrolling patients.

DIAGNOSIS AND PROGNOSIS

Histological markers

The glomerular histopathology in the IgAN is extremely variable, and its identification and reproducibility among different observers is essential to establish any relationship between renal pathology and disease evolution[11].

The glomerular abnormalities range from minimal abnormalities to mesangial hypercellularity, endocapillary hypercellularity, extra capillary hypercellularity, and segmental glomerulosclerosis.

The tubulointerstitial lesions may be near normal, but in some patients a tubular injury resulting in a fibro proliferative peritubular response is observed. In addition, several clinicopathological correlations have reported that the tubular atrophy is the most reliable

Table 1 Definitions of pathological variables used in the Oxford classification of immunoglobulin a nephropathy

Variable	Definition	Score
Mesangial hypercellularity	< 4 Mesangial cells/mesangial area = 0	M0 < 0.5
	4-5 Mesangial cells/mesangial area = 1	M1 > 0.5
	6-7 Mesangial cells/mesangial area = 2	
	> 8 Mesangial cells/mesangial area = 3	
Segmental glomerulosclerosis	Any amount of the tuft involved in sclerosis, but not involving the whole tuft or the presence of an adhesion	S0 = absent
		S1 = present
Endocapillary hypercellularity	Hypercellularity due to increased number of cells within glomerular capillary lumina causing narrowing of the lumina	E0 = absent
		E1 = present
Tubular atrophy/interstitial fibrosis	Percentage of cortical area involved by the tubular atrophy or interstitial fibrosis, whichever is greater	0%-25% - T0
		26%-50% - T1
		> 50% - T2

Table 2 Summary of studies correlating the Oxford classification for immunoglobulin a nephropathy with clinical outcomes

Study	Patients (*n*)	End point	Univariate analysis	Multivariate analysis
Coppo *et al*[19]	206 A, 59 C	Rate of eGFR decline	M, E, S T	M, E, S, T
Herzenberg *et al*[20]	143 A, 44 C	Rate of eGFR decline	Not done	E, S, T
Katafuchi *et al*[21]	702 A, C	ESRD	Not done	S, T
Zeng *et al*[22]	1026 A	Rate of eGFR decline	M, S, T	M, T
Shi *et al*[23]	410 A	ESRD	M, S, T	S, T
Edström Halling *et al*[24]	99 C	GFR reduction > 50%, ESRD	M, E, T	E
Shima *et al*[25]	161 C	eGFR < 60% mL/min per 1.73m^2	M, T	M, T
Coppo *et al*[26]	973 A, 174 C	Rate of eGFR decline	M, E, S, T	S, T
Alamartine *et al*[27]	183 A	Doubling of SCr or ESRD	E, S, T	None
El Karoui *et al*[28]	128 A	Rate of eGFR decline	Not done	T
Lee *et al*[29]	69 A	GFR reduction > 50%, ESRD	E, T	E
Kang *et al*[30]	197 A	GFR reduction > 50%, ESRD	T	T
Le *et al*[31]	218 C	eGFR reduction > 50%, ESRD	T, S	T

A: Adults; C: Children; eGFR: Estimated glomerular filtration rate; E: Endothelial hypercellularity; ESRD: End-stage renal disease; GFR: Glomerular filtration rate; M: Mesangial hypercellularity; S: Segmental sclerosis; Scr: Serum creatinine; T: Tubular atrophy/interstitial fibrosis.

marker of an adverse outcome[11].

Several histological classifications have been proposed in an attempt to provide a valuable grading of histological damage and a clinico-pathological relationship. Until recently, the classifications from Lee *et al*[12], Haas *et al*[13] and Wakai *et al*[14] has been used the most. All of these classifications have the weakness of not distinguishing between the histological markers of acute activity and chronic activity of the disease. As a consequence, they fail to provide useful information concerning therapy for the acute and evolving phase of the disease.

Later on, an international working group of over 40 pathologists and nephrologists developed an evidence-based and reproducible classification for IgAN[15]. Data were obtained from 265 patients affected by IgAN who were followed for 5 years. Four histological variables had an independent value in predicting renal outcomes: Mesangial hypercellularity scores (M), segmental glomerulosclerosis (S), endocapillary hypercellularity (E) and tubular atrophy/interstitial fibrosis (T). This study led to the formulation of the Oxford classification (Table 1).

The Oxford classification has some limitations that should be remarked as the authors themselves recognize. The study is retrospective and the material comes from different countries and different centers, each with a specific and different method of evaluating renal function. In addition, the median number of glomeruli with crescents was only 9% and no patient had more than 55% of glomeruli with crescents. As a consequence, as remarked by other studies[16] in this cohort the prognostic significance of crescents is poor. Other limitations of the Oxford classification is the lack of immunohistochemical findings as the authors recognize in a further study[17]. This lack in addition to other points claims for the need of more validation studies[18].

Indeed, the prognostic value of the Oxford classification required validation and, since the Oxford classification was published, at least 17 validation studies have been reported. Eight of these studies were able to validate the classification (Table 2), principally highlighting the relevance of T, S and M scores[19-26]. Five more studies apparently did not validate completely the Oxford classification[27-31].

Validation of the Oxford classification of the IgA (VALIGA) is one of the more recent validation studies[26]. This study involved 1147 patients from 13 European countries. The principal conclusions of the study were that M, S and T lesions independently predicted eGFR loss and lower survival rates, but the addition of M, S

Table 3 Potential biomarkers for immunoglobulin a nephropathy

Biologics	Source	Rationale
Galactose deficient IgA1	Serum	Core antigen of the pathogenic IgA1 immune complex; leads to activation of mesangial cells and glomerulonephritis
Glycan-specific IgG	Serum	Form glycan-dependent complex with galactose-deficient IgA1; alanine to serine substitution in complementary-determining region 3 of IgG heavy chain; able to differentiate IgA nephropathy patients from controls with 88% specificity and 95% sensitivity
Activated complement C3	Serum	Up-regulated level in 30% of patients; correlated with deteriorating renal function
FGF 23	Serum	FGF23 serum levels are significantly associated with IgAN progression
Soluble CD89	Serum	Low levels in patients with disease progression compared with those without disease progression
Mannose-binding lectin	Urine	Significantly higher in patients than healthy controls; associated with histopathologic aggravations such as mesangial hypercellularity, tubular atrophy, interstitial fibrosis
EGF and MCP-1	Urine	An EGF/MCP-1 ratio greater than 366.66 extends renal survival to at least 84 mo in a cohort of 44 patients
Proteomic pattern	Urine	High throughput characterization of 2000 polypeptide using capillary electrophoresis on-line coupled to a mass spectrometer
microRNA profile	Urine	Sequencing identified microRNA profiling that is specific to IgA nephropathy

IgA1: Immunoglobulin A1; IgG: Immunoglobulin G; FGF23: Fibroblast growth factor 23; IgAN: Immunoglobulin a nephritis; RNA: Ribonucleic acid; EGF: Epidermal growth factor; MCP-1: Monocyte chemotactic peptide-1.

and T lesions to clinical variables predicted progression only in patients not receiving immunosuppressive treatment.

Overall, although the studies to validate the Oxford classification system led to divergent findings, this classification offers physicians a simple tool to distinguish between active and chronic lesions[32] and is the only classification system created in a truly evidence-based manner[33]. In addition, the Oxford classification system should be considered a working classification, and meetings are been held to clarify the discrepancies among the different validation studies. Waiting for further results and clarifications, to date, the KDIGO guidelines[34] do not recommend the use of pathological findings to guide therapy and predict prognosis.

The addition of clinical data to the histological findings improved the ability to predict outcomes. Indeed, in a recent study[35], a new rule to predict the risk of developing ESRD in IgAN patients was developed and validated using clinical measures together with the Oxford classification.

Biological markers
Serum and urine biomarkers may be useful both for diagnostic and prognostic purposes.

Several authors[36,37] have formulated the "four hits" theory to explain the IgAN pathogenesis. Accordingly, in a four steps fashion, after an increase of galactose deficient circulating IgA1 (Gd-IgA1), there is an antibody production against these Gd-IgA1. Later on immunocomplexes are formed and may deposit in the kidney. Finally an inflammatory response is activated.

According to the four hits theory of IgAN pathogenesis, the diagnostic biomarker's usefulness decreases from hit 1 to hit 4, while, on the contrary, the prognostic value increases[38].

Table 3 summarizes the different biomarkers and their rationale in the diagnosis[39].

Serum galactose deficient immunoglobulin A1
Galactose deficient immunoglobulin A1 (Gd-IgA1) represents a core antigen of the pathogenic IgA1 immunocomplexes and leads to activation of mesangial cells. Principally, Gd-IgA1 represents a diagnostic marker. Data from studies considering Gd-IgA1 a prognostic marker are discordant. In one study, the serum levels of Gd-IgA1 were associated with disease progression[40]. In another study, the serum levels of Gd-IgA1 did not correlate with proteinuria and eGFR decline[41].

Serum anti-glycan antibodies
This biomarker correlates with the urine protein/creatinine ratio[42] and with disease progression towards ESRD[43].

Serum breakdown of complement C3 products
Complement activation is up-regulated in 50% of patients and correlates with a decrease in renal function[44-46]. Additionally preliminary studies have documented in IgAN the association of glomerular C4d deposition with serum creatinine, proteinuria and histological damage[47]

Fibroblast growth factor 23
Fibroblast growth factor 23 (FGF23) is a circulating hormone involved in phosphate homeostasis. In a recent study, FGF23 levels were significantly associated with IgAN progression[48].

CD89-IgA complexes
The deposition of CD89-IgA complexes may facilitate mesangial cell activation. A study reported that IgAN patients without disease progression had high levels of soluble CD89, whereas patients with disease progression had low levels of soluble CD89[49].

In addition to the serum biomarkers, urinary biomarkers may also be useful both in the diagnosis of IgAN and the prognosis .

The urinary mannose-binding lectin[50] is a biomarker for predicting IgAN progression. Indeed, it is associated with the worsening of histopathologic lesions such as mesangial hypercellularity, tubular atrophy and interstitial fibrosis.

In a small cohort[51], a urinary epidermal growth factor/monocyte chemotactic peptide ratio greater than 366.66 was related to an improvement in the renal survival rate over the long term.

The relevance of urine proteomics as an alternative to single biomarkers has been evaluated[52,53]. The usefulness of proteomics as a diagnostic tool has been documented, but its value as a prognostic factor remains to be evaluated.

Several studies have evaluated the role of small microRNAs in the diagnosis and the prognosis of IgAN[54].

MicroRNAs are short, noncoding RNA molecules that regulate gene expression. Micro RNAs such as 18-5 p, 29 c, 133 a, 133 b, 148 b, 185, 192 and 200 c have been documented to exert a role in the pathogenesis of IgAN. Their level in urinary excretion may be elevated in the course of the disease and may represent a useful diagnostic tool. The prognostic value remains to be evaluated, even though the relationship between the urinary levels of miRNA 146 and miRNA 155 and proteinuria and lower GFR have recently been documented[55].

Many biological markers have been described principally as a possible diagnostic tool. Some papers have also reported their usefulness in prognosis and have described their correlation with disease evolution. However, none of these approaches has been properly confirmed as a valuable predictor of clinical outcomes, and their superiority with respect to the clinical markers is still to be proven.

Clinical markers

To date, clinical prognostic markers remain as the most reliable predictors of IgAN evolution.

Principally, they include an impaired GFR, sustained hypertension and proteinuria[56,57]. Longitudinal trends in blood pressure (BP) and proteinuria are both associated with disease progression[58,59]. In a prospective study on 332 IgAN patients[59], proteinuria > 1 g/d, and hypertension > 140/90 mmHg, when associated with severe histological lesions, allowed the calculation of a risk score predicting death or ESRD 10 years to 20 years after disease onset. Another study, based on retrospective data from 600 IgAN Chinese patients[60], identified four baseline variables with an independent risk of ESRD evolution; *i.e.,* GFR, serum albumin, hemoglobin and systolic BP. Recently, looking for the IgAN outcome predictors, a study on a multiethnic United States cohort documented that the baseline eGFR was the strongest predictor of ESRD[61]. High body mass index and smoking have also been identified as predictors of poorer outcomes in IgAN[62,63]. These factors, however, are not specific for IgAN, but are common to any glomerulonephritis.

By contrast, the degree of hematuria, which is a typical manifestation of IgAN, does not have a predictive value. As already mentioned the clinical presentation with AKI accompanying macroscopic hematuria doesn't necessarily mean crescentic IgAN but may be the expression of acute tubular necrosis spontaneously resolving.

In summary, several histological, biological and clinical markers have been proposed as predictors of IgAN outcomes and, as a consequence, are useful for suggesting therapeutic measures and monitoring their effects. However, to date, neither histological nor biological markers have documented a clear superiority over the more simple clinical markers[10].

THERAPY

From a therapeutic point of view, IgAN patients at diagnosis should be divided into three groups[10] and the therapeutic approaches differ according IgAN groups. (1) low risk patients: These are subjects with normal GFR, no hypertension and minor urinary abnormalities (proteinuria < 0.5 g/d +/- isolated microhematuria). These patients do not require treatment but should be checked annually or biannually for at least 10 years. Monitoring is recommended to check any disease evolution. In the case of disease evolution, therapeutic measures should be adopted as described below; (2) intermediate risk patients have a proteinuria > 0.5-1 g/d that may be associated with hypertension and a reduced GFR. These patients should receive optimized supportive therapy and should be strictly monitored. A corticosteroids course and/or immunosuppressive treatment might be added if proteinuria increases or GFR declines; and (3) high risk patients show a rapid decrease in the GFR that may be associated with nephritic syndrome or crescentic glomerulonephritis. These findings may be already present at IgAN diagnosis or may develop during the disease evolution. In addition to supportive treatment, corticosteroids and immunosuppression should be considered for these high risk patients.

Supportive care

Supportive care is recommended by KDIGO guidelines[34] for any IgAN patient at risk of disease evolution.

The supportive care includes several measures aimed to control the progression of any glomerulonephritis, among which is IgAN (Table 4)[64].

The mainstay of supportive treatment in IgAN is the control of BP and control of the renin-angiotensin system (RAS)[65].

A review of 11 RCTs, documented that treatment with angiotensin converting enzyme inhibitors (ACEI) or with angiotensin receptor blockers (ARB) significantly reduced proteinuria and had a renoprotective effect with respect to the controls[66]. These data were confirmed by a meta-analysis that reviewed 6 RCTs[67].

Table 4 Supportive therapy of immunoglobulin a nephropathy

Level 1	Control blood pressure (sitting systolic BP in the 120 s)
	ACE inhibitor or ARB therapy with up-titration of dosage or combination ACE inhibitor and ARB therapy
Level 2	Control protein intake
	Restrict NaCl intake/institute diuretic therapy
	Control each component of the metabolic syndrome
	Aldosterone antagonist therapy
	Beta-blocker therapy
	Smoking cessation
Other measures	Allopurinol therapy
	Empiric NaHCO₃ therapy, independent of whether metabolic acidosis is present or not
	Avoid NSAIDs altogether, or no more than once or twice weekly at most
	Avoid prolonged severe hypokalemia
	Avoid phosphate cathartics
	Ergocalciferol therapy to correct vitamin D deficiency
	Control hyperphosphatemia and hyperparathyroidism

ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; NaCl: Sodium chloride; NaHCO₃: Sodium bicarbonate; NSAID: Non-steroidal anti-inflammatory drug.

More recently, the beneficial effect of Aliskiren, a direct renin inhibitor, has been documented by two studies[68,69]. Its protective effect principally is a consequence of proteinuria reduction.

In addition, a wide Cochrane review of 56 RCTs including 2838 IgAN patients[70] documented that antihypertensive agents, in particular the RAS inhibitors were more powerful renoprotective agents among the non-immunosuppressive therapies. Indeed, the effect of antihypertensive agents was compared with treatments such as fish oil supplementation, antiplatelets/anticoagulants agents and other treatments such as statins, phenytoin, herbal medicine, vitamin E and sodium cromoglycate.

Other controversial non-immunosuppressive treatments

Fish oil supplementation is an old therapy with varied results.

In a meta-analysis of fish oil therapies, no significant beneficial result was observed[71]. In the largest RCT with fish oil, an improvement in disease evolution was observed in treated patients[72], but these results were not confirmed in a more recent RCT[73].

Antiplatelet and anticoagulant based therapy is widely used in Asia. A small study documented some efficacy with dipiridamole and warfarin, but the study did not have a control group[74].

In a recent study[75] a beneficial effect was observed using statins. The study was small, not controlled, and the effect of statins on IgAN remained unclear.

In summary, as documented by the above mentioned Cochrane review[70] and after comparing the different non-immunosuppressive treatments, the only documented beneficial effect is exerted by the antihypertensive drugs, and this effect seems to be mediated by proteinuria reduction. In a recent meta-analysis[76], combination therapy with ACEI and ARB seems to achieve more benefits, even if the long-term effects still need to be documented.

Tonsillectomy

The efficacy of tonsillectomy alone or associated with immunosuppression has been a matter of discussion, and discordant results have been reported for a long time. The rationale of tonsillectomy in IgAN prevention and/or treatment is the elimination of an important source of pathogens by removing tonsil crypts. Indeed, a recent study[77] has indicated that palatine tonsils are probably a major site of Gd-IgA1 producing cells. In some patients these cells may be largely present in other lymphoid organs, and this fact might explain the diverging results of tonsillectomy.

Tonsillectomy associated with pulse steroids or other immunosuppressants is largely used in Japan, as documented by several retrospective studies[78,79]. In addition, a recent meta-analysis of seven non-randomized studies (6 in Japan and 1 in China) documented an overall beneficial effect of tonsillectomy plus corticosteroids[80]. In another meta-analysis from China, of 14 studies including 1794 patients[81], the authors concluded that tonsillectomy may induce clinical remission, but the adjustment for confounding variables could not be performed because the majority of the studies included retrospective cohorts of patients.

Recently, the first national multicenter RCT from Japan failed to demonstrate any superior effect of tonsillectomy associated with pulse steroids over pulse steroids alone[82].

Because other studies on Chinese[83] and Caucasian patients[84,85] did not confirm the tonsillectomy beneficial effect, waiting for an adequately powered RCT tonsillectomy should not be recommended. The KDIGO suggested that tonsillectomy should not be performed to treat IgAN[8]. A retrospective study on 1147 European patients with IgAN failed to demonstrate a significant correlation between tonsillectomy and renal function decline[86].

Corticosteroids

To date, the KDIGO guidelines[34] suggest a 6 mo course

of corticosteroids only for those patients at intermediate risk of having persisting proteinuria > 1 g/d and with a GFR between 30 mL/min per 1.73 m^2 and 50 mL/min per 1.73 m^2, after optimization of supportive therapy. Several studies have been performed to evaluate the usefulness of corticosteroid therapy in IgAN. According to several studies[87-90], steroids have a renoprotective effect. In some of these studies, the beneficial effect seems to be related to a long course therapy or to a higher dose. Other studies did not confirm a steroid related beneficial effect[91] or highlight the problem of corticosteroid side effects[92].

A Cochrane review on immunosuppressive therapy in IgAN[93] analyzed 32 studies comprising 1781 patients. Six of these studies analyzed the effects of steroids. A renoprotective effect was observed comparing steroids *vs* placebo or no treatment. Unfortunately, all the aforementioned studies did not answer a number of questions such as the following: Were steroids also effective for patients with a GFR < 30 mL/min per 1.73 m^2? What is the best steroid dosage and regimen to avoid side effects? RCTs that are ongoing such as the Supportive Versus Immunosuppressive Therapy of Progressive IgA Nephropathy (STOP IgAN)[94] and the Therapeutic Evaluation of Steroids in IgA Nephropathy (TESTING) study[95] might provide definitive evidence for a role of corticosteroids in the treatment of IgAN.

Recently, the VALIGA study retrospectively evaluated the role of corticosteroids in IgAN[96]. The authors observed that corticosteroids reduced proteinuria and the rate of renal function decline. In addition, these benefits also involved patients with an eGFR < 50 mL/min. The results of this study should encourage nephrologists to further investigate corticosteroids efficacy in patients with low baseline GFR[97].

Corticosteroids in association with other therapies
The already cited Cochrane review[93] highlighted the higher efficacy of corticosteroids given in association with ARB with respect to corticosteroids alone or ARB alone.

Other studies[80] documented the higher efficacy of tonsillectomy plus steroids with respect to tonsillectomy alone or steroid therapies alone.

The association of steroids with other immunosuppressants has been principally used for high risk patients.

Association of cyclophosphamide and corticosteroids offered different results
The association of cyclophosphamide and corticosteroids has been principally examined in studies concerning patients with progressive renal deterioration or with crescentic IgAN[98-100]. The combined cyclophosphamide/steroid therapy may benefit patients at a high risk of renal failure. The limitation of these studies is that they are small, often retrospective, and side effects represent a serious concern. The KDIGO guidelines[34] do not recommend such treatment for the vast majority

of IgAN patients. A possible role is suggested by the guidelines only for patients with crescentic IgAN and rapidly decreasing renal function.

Similarly, the use of azathioprine (AZA) in addition to corticosteroids is not recommended. Indeed, in two studies from Pozzi *et al*[101,102] the addition of AZA to corticosteroids did not provide any beneficial result in patients with ongoing severe chronic renal failure.

The aforementioned Cochrane review on immunosuppressants in the treatment of IgAN highlighted that the use of such treatments had low evidence and was not powerful to guide clinical practice. In addition, evidence on mortality, infections and cancers is sparse or of low quality.

The use of calcineurine inhibitors in addition to corticosteroids has been tested in some recent small RCTs[103,104]. Some benefit has been reported for the reduction of proteinuria, but the addition of cyclosporine in some patients caused a serum creatinine increase and a higher infection incidence.

Other immunosuppressants
In a recent study, Kim *et al*[105] compared tacrolimus (TAC) with ACEI/ARB therapy. In this small study, TAC reduced proteinuria in IgAN patients, but the follow-up was too short to draw any conclusion.

Mycophenolic mofetil (MMF), in addition to its immunosuppressive action on lymphocytes, has been documented to reverse IgA1 aberrant glycosylation, up-regulating the core 1 beta 3 - GalT-specific molecular chaperone that is impaired in IgAN[106].

The first RCT of MMF was conducted on Chinese patients with severe IgAN[107]. The effects on proteinuria were significant at 18 mo. At the same time, two other European studies failed to document a beneficial effect of MMF[108,109]. These data raised the possibility of a different response to MMF in different ancestral cohorts.

Later on, three other Chinese studies reported an improved outcome in IgAN patients treated by MMF[110-112]. In addition to the improved outcomes of patients treated with MMF, the study by Tang *et al*[111] documented that MMF inhibited IgA binding to mesangial cells. Diverging results have also been reported in more recent studies. In an Italian study, MMF and steroids reduced proteinuria and improved outcomes in IgAN patients at risk for progression[113]. In another study, MMF therapy was effective for IgAN children with nephritic syndrome and resistant to steroid treatment[114].

A recent study from the United States was not able to document any MMF related beneficial effect[115], but the study had the limitation of enrolling few patients and had a short follow-up.

A Chinese review on the efficacy and safety of MMF treatment in IgAN recognized that high quality RCTs with large sample sizes and a long follow-up are needed to evaluate the MMF efficacy in IgAN[116]. To date, the KDIGO guidelines do not recommend the use of MMF in IgAN patients.

Therapy for recurrence of IgAN after kidney transplantation

Post-transplant recurrence of IgAN is common. As prevention and treatment of acute and chronic rejection is continuously improving, renal disease recurrence on the graft may become a relevant cause of graft loss over the long term[117]. However, none of the current available immunosuppressive drugs are able to prevent the histological recurrence of IgAN[118,119]. Patients with recurrent IgAN after transplantation should be given optimized supportive care. A Japanese study suggested that a preoperative tonsillectomy might not affect the recurrence of IgAN[120].

A study from Berthoux *et al*[121] suggested that an induction therapy with ATG might have a protective role against IgAN recurrence, but these results have not been confirmed. Registry data from the Australia and New Zealand Dialysis and Transplant Registry documented that the corticosteroids given continuously after transplantation significantly reduced the risk of IgAN recurrence[122]. An analysis of the United States Renal Data System similarly documented a protective effect of corticosteroids after IgAN recurrence in renal transplant patients[123]. A retrospective study documented no benefit using MMF instead of AZA as an antimetabolite drug after transplantation[124].

New therapies and ongoing clinical trials

New therapies: *In vitro* studies documented that peroxisome proliferator-activated receptor-gamma (PPAR-gamma) agonist attenuates inflammation in tubular epithelial cells in IgAN[125]. The additive effect of PPAR-gamma agonist and ARB has been confirmed in an animal model of IgAN[126].

A new enteric formulation of the locally acting glucocorticoid budesonide, designed to release the active compound in the ileo-cecal region, has been used to treat IgAN and was effective in reducing proteinuria and slightly increasing eGFR[127]. The aim of a locally releasing compound is to limit the corticosteroid side effects. Based on these data, a multicenter phase Ⅱb trial (NEFIGAN) is currently ongoing in Europe.

Complement activation is involved in IgAN tissue injury. Rituximab has been successfully used as rescue therapy in IgAN with rapid progression[128]. However, in another study, rituximab, given as a single dose at the beginning of the therapy, failed to reduce proteinuria and to inhibit GFR decline[129].

Bortezomib is a proteasome inhibitor approved for the treatment of multiple myeloma and tested to decrease antibody levels in hyperimmune patients in renal transplantation. The rationale for using Bortezomib in the treatment of IgAN relies on the fact that, in IgAN, a switch from proteasome (PS) to immune PS has been observed, suggesting a hyperactivation of the PS system. In addition, an increased nuclear translocation of the p50 active subunit of NF-κB has been observed in these patients[130,131]. A phase Ⅲ clinical trial is to date ongoing.

Spleen tyrosine kinase (SYK) is an intracellular protein tyrosine kinase involved in cell signaling downstream of the immunoreceptors. Recently, the involvement of the SYK in the inhibition of IgA1 stimulation of human mesangial cells and in the pathogenesis of IgAN has been documented[132]. A RCT with a selective oral SYK inhibitor in patients with IgAN is currently ongoing.

Recently in China the efficacy and safety of Leflunomide given in association with steroids has been evaluated. In a first RCT the efficacy of Leflunomide was evaluated in IgAN patients affected by nephritic syndrome[133]. In this context leflunomide resulted a safe and effective drug for the treatment of IgAN. More recently a larger number of IgAN patients were enrolled in a RCT to receive Valsartan combined with clopidogrel and/or leflunomide for the treatment of progressive IgAN[134]. The treatment with Valsartan combined with clopidogrel and leflunomide resulted in a reduction of proteinuria and of renal function deterioration.

Ongoing clinical trials for IgAN treatment: Several clinical trials for IgAN are ongoing. As mentioned previously, only the active ongoing clinical trials that are recruiting patients will be discussed.

Clinical trials may involve old drugs given with new strategies or new drugs not yet on the market.

Two RCTs are testing the efficacy of MMF in patients with IgAN. One RCT[135] includes patients with proteinuria > 1 g/d already in treatment with ARB. The purpose of the RCT is to evaluate the efficacy of MMF in reducing proteinuria and preserving renal function compared to corticosteroids. The other trial (MAIN)[136] is enrolling patients with advanced IgAN. The purpose of the study is to evaluate MMF compared to losartan alone in patients treated with the maximum tolerated daily dose of losartan.

Four RCTs are evaluating the effects of corticosteroids on IgAN.

Apart from the already cited TESTING study[95], a Chinese RCT[137] is evaluating the efficacy and safety of steroids in IgAN patients with active pathological lesions. The TOPplus-IgAN RCT[138] is evaluating the effects of prednisone plus cyclophosphamide in patients with advanced stage IgAN and is evaluating combination therapy with respect to corticosteroids alone. The first available data from the STOP-IgA[94] reported that appropriate supportive care blunted the effect of immunosuppression in proteinuric IgAN patients.

The adrenocorticotropic hormone (ACTH) has been used in RCTs for the treatment of several diseases, among which is glomerulonephritis. Indeed, ACTH seems to exert a non-specific antiproteinuric effect rather than a specific effect. Bomback *et al*[139] treated several proteinuric patients, among which 5 patients were affected by IgAN with proteinuria resistant to other therapies.

To date, two studies are testing the gel formulation of ACTH in the treatment of IgAN at a high risk of progression[140].

As mentioned previously, rituximab has been used in the treatment of IgAN. To our knowledge, the only RCT on rituximab[141] is not enrolling patients.

CCX168 is an orally administered, specific small molecule inhibitor of the C5a receptor. Trials with CCX168 are ongoing in the treatment of the atypical hemolytic uremic syndrome and antineutrophils cytoplasmic antibodies vasculitis. A phase Ⅱ study is enrolling patients to evaluate CCX168 efficacy in reducing proteinuria in IgAN with persistent proteinuria despite supportive therapy with a maximally tolerated RAS blocker[142].

Blisibimod is a selective antagonist of the B-cell activating factor and is being tested in lupus nephritis. A RCT (BRIGHT-SC) is evaluating blisibimod in a phase Ⅱ/Ⅲ trial in proteinuric patients affected by IgAN[143].

The aforementioned enteric budesonide is being evaluated for the treatment of IgAN in a European multicenter RCT[144].

A pilot study on Velcade (bortezomib)[145] in IgAN has the purpose of investigating the ability of bortezomib to induce complete or partial remission in patients with severe IgAN.

Fostanatimib is a selective inhibitor of SYK that is involved in the pathogenesis of IgAN. A phase Ⅱ RCT is, to date, ongoing with the purpose of determining whether fostanatimib is safe and effective in the treatment of IgA nephropathy[146].

Finally, two Chinese RCTs are evaluating the efficacy of two traditional Chinese medicines; *i.e.,* Abelmoschus Manihot[147] and Tripterygium Wilfordii HOOK[148], in the treatment of IgAN. The former RCT is comparing the study drug with losartan, and the latter with MMF.

CONCLUSION

Patients affected by IgAN may present extremely different clinical aspects at diagnosis. The disease evolution also may differ ranging from a stable course of disease with no evolution to a disease rapidly evolving to ESRD. Accordingly, the therapeutic approaches may vary from only the need for frequent controls to check for disease evolution to careful supportive care for patients with clinical signs, from urinary abnormalities, hypertension and reduced GFR to intensive treatment in patients with rapid evolution.

Because the so called "silent majority" does not have any disease evolution, the major problem is to identify those patients who will have disease evolution in the future. Histological and biological markers have been proposed in an attempt to identify such patients, but, to date, the clinical markers represent the optimal tool for monitoring IgAN patients.

Patients with stable disease with no sign of disease evolution only need to be monitored. Patients with slow evolving disease and low level proteinuria, in addition to being monitored, need optimal supportive care. In recent years, treatment with corticosteroids may be useful for such patients and is recommended by the guidelines.

Intensive treatment with corticosteroids and other immunosuppressants should only be reserved for patients with rapidly progressive disease or with a histological picture of extracapillary glomerulonephritis or with nephrotic proteinuria.

Several RCTs concerning new drugs are included in the international registries, but only some trials are enrolling patients.

In any case, these new drugs should be reserved for high risk patients and should not be used until validated in large studies for a long period of time.

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