In Crescentic IgA Nephropathy, Fractional Excretion of IgG in Combination with Nephron Loss Is the Best Predictor of Progression and Responsiveness to Immunosuppression

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Background and objectives: The aim of this study was to evaluate the relationship between proteinuric markers (urinary excretion of IgG, α2-macroglobulin, α1-microglobulin) and serum creatinine (sCr), histologic lesions, progression, and immunosuppression responsiveness in crescentic IgA nephropathy.

Design, setting, participants, & measurements: Fractional excretion of IgG (FEIgG) and of α1-microglobulin and urinary excretion of α2-macroglobulin were evaluated in 37 patients, 23 treated with steroids and cyclophosphamide. For assessment of the effective tubular load of proteins in surviving nephrons, new markers that take into account not only the absolute excretion value but also nephron loss were obtained dividing proteinuric markers for percentage of nonobsolescent glomeruli (surviving glomeruli [SG]). For each parameter, low- and high-risk groups were defined according to cutoffs with the highest sensitivity and specificity for progression (ESRD/doubling sCr) assessed by receiver operating characteristic analysis; follow up was 60 ± 40 mo.

Results: FEIgG/SG is the most powerful progression predictor: 5 *versus* 83% in all patients; in treated patients, 0 *versus* 89%, increased to 0 *versus* 100% by sCr and FEIgG/SG in combination (low risk: both markers or only one below cutoff ($n = 15$); high risk: both markers above cutoff ($n = 8$). The nonprogressors showed at last observation 65% proteinuria reduction and 10% sCr reduction.

Conclusions: In crescentic IgA nephropathy, FEIgG/SG, which evaluates altered size selectivity in relation to nephron loss, is the best progression predictor. In treated patients, progression prediction was increased by FEIgG/SG and sCr in combination. Treatment may be restricted to low-risk patients.

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The crescentic variant of IgA nephropathy (cIgAN) with histologic features similar to those observed in Schönlein-Henoch or ANCA-related renal vasculitis is characterized by more frequent nephrotic syndrome and renal functional impairment, more severe global glomerulosclerosis and tubulointerstitial damage, and higher rate of progression to renal death in comparison with noncrescentic IgAN (1,2). Treatment that is appropriate to prevent progression has not been clearly identified. Few small, nonrandomized studies have evaluated the efficacy of intravenous and oral steroids and oral or intravenous cyclophosphamide (3–9), but no firm conclusions can be drawn about the best type of therapy and the clinical and laboratory features that are able to predict treatment responsiveness. In glomerulonephritis, "crucial to the question of therapy is the ability to predict outcome in a patient as early and accurately as possible and ideally based on modifiable factors. Only after this assessment is made can we logically determine the risk *versus* benefit of treatments" (10). Proteinuria is one of the most powerful predictors of progression in IgAN; surprisingly, no one study has analyzed in cIgAN the urinary excretion of single proteins to evaluate their relationship with renal function and histologic lesions and to assess whether some "glomerular" and/or "tubular" component of proteinuria predicts outcome and therapy responsiveness better than other, widely known predictors (renal functional impairment, proteinuria, global glomerulosclerosis, extent of tubulointerstitial damage). The aim of this study was to analyze in 37 patients with cIgAN the fractional excretion of IgG (FEIgG) and α1-microglobulin (FEα1m) and urinary excretion of α2-macroglobulin (uα2m/g uCr) and their relationship with renal function, histologic lesions, functional outcome, and responsiveness to therapy.

Materials and Methods

Patients

Between January 1992 and December 2004, 168 patients had a diagnosis of IgAN in our nephrologic unit and met each of the following

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criteria: (*1*) Minimum of six glomeruli on light microscopy, (*2*) predominant mesangial IgA deposition by immunofluorescence, and (*3*) no signs of systemic involvement (Schönlein-Henoch purpura, systemic lupus erythematosus, chronic liver disease). Thirty-seven (22%) patients with cellular crescents in 4 to 63% of glomeruli, associated or not with segmental necrotizing lesions, are the object of this study; inclusion criterion was presence of cellular crescents in at least one glomerulus to evaluate clinical characteristics and prognostic value of every percentage of cellular crescents. Clinical presentation was as follows: macroscopic hematuria 27%, isolated urinary abnormalities 41%, nephrotic proteinuria (≥3.0 g/d) 32%, impairment of renal function (serum creatinine [sCr] ≥ 1.4 mg/dl) 46%, hypertension (BP ≥ 140/90 mmHg) 54%, and follow-up 60 ± 40 mo. The clinical and demographic features are reported in Table 1. This study adhered to the Declaration of Helsinki. All patients gave informed consent to treatment of data.

Renal Biopsy

Renal biopsy was performed as described previously (11); indication for biopsy included also minimal urinary abnormalities or advanced renal failure. For each biopsy, the following features were evaluated: percentage of global glomerular sclerosis (GGS); extent of tubulointerstitial damage (TID) semiquantitatively graded by a score (TID score) from 0 to 2 if tubular atrophy, interstitial infiltration and fibrosis were absent (0), focal (1), or diffuse (2); total score from 0 to 6 (TID)); percentage of glomeruli with crescents. The crescents were classified as cellular or fibrous; 21 (57%) patients had only cellular crescents in 4 to 63% of glomeruli (mean 25 ± 17%), and 16 (43%) patients had mixed pattern of cellular (13 ± 11%) and fibrous (12 ± 7%) crescents; cellular crescents were segmental in 36 patients and circumferential in one.

Measurement of Urinary Proteins

For each patient, 24-h urine collection and second morning urine sample were obtained before biopsy. Urinary proteins were measured by the Coomassie blue method (modified with SDS) and expressed in g/24 h (24hP). sCr and urinary creatinine (uCr) were measured by automated methods and expressed in mg/dl. IgG (molecular weight 150 kD) and α1-microglobulin (α1m; molecular weight 31.8 kD) were measured in serum and second morning urine samples as described previously (12); FEIgG and FEα1m, expressed per 100 ml of creatinine clearance, were calculated according to the formula (urinary protein/serum protein × sCr/uCr) × 100. α2-Macroglobulin (α2m; molecular weight 720 kD), measured by immunonephelometry in second morning urine samples, was expressed in mg/g of urinary creatinine (uα2m/g uCr).

The expression of total proteinuria or proteinuria components as absolute values does not reflect the effective protein load in surviving nephrons; to assess with greater precision the effective tubular load of proteins in surviving nephrons, total proteinuria and proteinuria components may be divided for the percentage of nonglobally sclerotic glomeruli (defined as surviving glomeruli [SG]); thus, we created new proteinuric markers (FEIgG/SG, FEα1m/SG, uα2m/g uCr/SG, and 24hP/SG) dividing absolute values for the percentage of SG. The ability of these markers to improve prediction of functional outcome was evaluated. Segmental sclerosis, present in 13 ± 13% of glomeruli (range 0 to 45%), marker of partially surviving glomeruli, was not taken into account for the difficulty and imprecision of its quantitative evaluation.

End Point and Risk Factors

The end point for progression was the combination of ESRD and doubling of sCr. Several baseline risk factors (RFs) were evaluated for ability to predict progression: sCr, 24hP, 24hP/SG FEIgG, FEIgG/SG, FEα1m, FEα1m/SG, uα2m/g uCr, uα2m/g uCr/SG, GGS, TID, and cellular crescents. For each RF, the patients were divided in two groups with "low" and "high" risk for progression according to a cutoff with the highest sensitivity and specificity for progression assessed by receiver operating characteristic (ROC) analysis.

Table 1. Comparison of baseline demographic, clinical, and laboratory characteristics of 111 patients without and 37 patients with cellular crescents[a]

Characteristic	Noncrescentic IgAN		cIgAN	
	Value	*P*	Value	Range
n	111		37	
Age	39 ± 15	0.0010	30 ± 11	15 to 68
Gender (M/F)	73/38	0.9200	24/13	
sCr	1.33 ± 0.85	0.0100	2.08 ± 1.85	0.57 to 8.24
24hP	0.75 ± 0.81	<0.0001	3.04 ± 3.03	0.20 to 14.30
uα2m/g uCr	0.41 ± 1.36	<0.0001	9.00 ± 12.80	0.00 to 52.50
FEIgG	0.005 ± 0.020	<0.0001	0.058 ± 0.120	0.000 to 0.511
FEα1m	0.136 ± 0.241	0.0050	0.412 ± 0.675	0.000 to 2.590
No. of glomeruli in renal biopsy	18 ± 9	NS	17 ± 7	6 to 63
GGS (%)	15 ± 19	0.0040	21 ± 16	0 to 54
TID score	1.8 ± 1.7	<0.0001	3.4 ± 1.7	0.0 to 6.0
Cellular crescents (%)	0	<0.0001	19 ± 15	4 to 63
Fibrous crescents (%)	0	<0.0001	5 ± 7	0 to 24
High BP	42%	0.2200	54%	
Follow-up (mo)	50 ± 32	NS	60 ± 40	2 to 135

[a]24hP, 24-h proteinuria; FEα1m, fractional excretion of α1-microglobulin; FEIgG, fractional excretion of IgG; GGS, global glomerular sclerosis; sCr, serum creatinine; TID score, tubulointerstitial damage score; uα2m/g uCr, urinary excretion of α2-macroglobulin expressed in mg/g urinary creatinine.

Treatment

Twenty-three patients were treated soon after biopsy with immunosuppression on the basis of clinical and/or histologic characteristics: cellular crescents in ≥10% of glomeruli and/or rapidly progressive or chronic renal failure and/or nephrotic proteinuria. The treatment was three methylprednisolone pulses (0.5 to 1.0 g intravenously for 3 consecutive days at start of treatment [lower dosage in advanced renal failure]) followed by prednisolone 0.5 mg/kg body wt for 6 mo with monthly tapering; 19 patients were treated with three intravenous cyclophosphamide pulses (0.5 to 1.0 g [lower dosage in advanced renal failure]) at the beginning of the first, third, and fifth months) and four patients with oral cyclophosphamide (50 to 100 mg/d for 2 mo). Patients treated with steroids alone ($n = 3$) or supportive therapy ($n = 8$) were excluded from the analysis that evaluated the relationship between RFs and therapy responsiveness.

Statistical Analysis

Baseline functional, proteinuric, and histologic parameters were compared among patients with and without cellular crescents by χ^2 test for categorical variables and by the nonparametric Kruskal-Wallis test for continuous variables. Correlation between histologic and proteinuric parameters was assessed by Spearman correlation coefficient. To find out the most powerful predictors of postbiopsy progression, we constructed ROC curves (13). The area under the curve (AUC) was used to measure the accuracy of each factor in discriminating between patients who did or did not have postbiopsy progression. The cutoff for each factor is chosen so that it maximizes sensitivity and specificity. Differences in disease progression rates according to the previously defined risk groups for each factor were assessed by log-rank test. We then used Cox proportional hazard regression to evaluate the independent effect of the most predictive independent factors on disease progression. Survival analyses were carried out both on the whole group of 34 patients with cellular crescent and in the subgroup of 23 patients who were treated with steroids and cyclophosphamide. Baseline and final values of 24hP and sCr were compared in nonprogressive treated patients by the Wilcoxon signed rank test and the McNemar test.

Results

Comparison of Patients with and without Cellular Crescents

The 37 patients with cellular crescents were compared with 111 patients without any type of crescent; the results are reported in Table 1. The patients with cellular crescents had significantly higher values of baseline functional, proteinuric, and histologic parameters except hypertension. The highest differences between patients with and without cellular crescents were observed for uα2m/g uCr (8.1-fold higher in patients with cellular crescents), FEIgG (six-fold), and FEα1m (three-fold).

RFs Associated with "Prebiopsy" Progression

Seventeen (46%) patients had at biopsy renal functional impairment (sCr ≥ 1.40 mg/dl; mean sCr 3.27 ± 2.21 mg/dl; range 1.43 to 8.24) that may be considered as dependent on progression of disease from its onset to the time of biopsy. The correlations between baseline sCr and proteinuric and histologic parameters are reported in Table 2. FEIgG ($r = 0.749$) and FEα1m ($r = 0.834$) showed a degree of correlation higher than 24hP ($r = 0.490$) and α2m/g uCr ($r = 0.348$); GGS ($r = 0.518$) and TID score ($r = 0.700$) showed a high degree of correlation with sCr, whereas cellular crescents did not show a significant correlation ($r = 0.208$).

Table 2. Factors associated with prebiopsy progression: correlation between baseline serum creatinine, proteinuric, and histologic parameters

Risk Factors	*r*	*P*
FEα1m	0.834	<0.0001
FEIgG	0.749	<0.0001
TID score	0.700	<0.0001
GGS	0.518	0.0010
24hP	0.490	0.0021
uα2m/g uCr	0.348	0.0346
Cellular crescents	0.208	0.2140

Relationship between Proteinuric and Histologic Parameters

The correlations between histologic and proteinuric parameters are reported in Table 3. GGS was correlated with FEIgG ($r = 0.536$), FEα1m ($r = 0.454$), and 24hP ($r = 0.350$) but not with uα2m/g uCr ($r = 0.162$). TID score was correlated with FEIgG ($r = 0.725$), FEα1m ($r = 0.664$), 24hP ($r = 0.570$), and uα2m/g uCr ($r = 0.497$). Cellular crescents were correlated with 24hP ($r = 0.488$), FEIgG ($r = 0.414$), and uα2m/g uCr ($r = 0.336$) but not with FEα1m ($r = 0.263$). In conclusion, FEIgG was highly correlated with all of the histologic lesions.

Factors Associated with Postbiopsy Progression and Cutoff Points for Each Parameter

The RFs associated with postbiopsy progression and the cutoff point for each parameter with the highest sensitivity and specificity for progression were assessed by ROC analysis. In Table 4 are reported the AUC, the cutoffs with the highest sensitivity and specificity for progression, and the misclassification rate. sCr shows the largest area (0.921), followed by

Table 3. Correlation between proteinuric and histologic parameters[a]

Proteinuric RF	GGS	TID Score	Cellular Crescents
FE IgG			
r	0.5360	0.7250	0.4140
P	0.0006	<0.0001	0.0100
FE α1m			
r	0.4540	0.6640	0.2630
P	0.0048	<0.0001	0.1100
24 h P			
r	0.3500	0.5700	0.4880
P	0.0300	0.0002	0.0020
uα2m/g uCr			
r	0.1620	0.4970	0.3360
P	0.3300	0.0017	0.0400

[a]RF, risk factors.

Table 4. Risk factors associated with postbiopsy progression: AUC, cutoff values for progression, sensitivity and specificity, and misclassification rate[a]

RFs	AUC	Cutoff	Sensitivity (%)	Specificity (%)	Misclassification Rate (%)
sCr	0.921	≥1.74000	92	82	14
FEIgG/SG	0.901	≥0.00034	91	92	9
FEIgG	0.891	≥0.01600	91	78	17
FEα1m/SG	0.891	≥0.00400	91	87	11
FEα1m	0.875	≥0.23000	91	83	14
TID score	0.862	≥3.00000	100	57	29
uα2m/g uCr/SG	0.828	≥0.11000	73	90	14
uα2m/g uCr	0.806	≥5.49000	73	74	26
GGS	0.781	≥20%	82	70	26
24hP/SG	0.783	≥0.03400	82	70	26
24hP	0.751	≥2.72000	73	74	26
Cellular crescents	0.623	≥17%	64	58	40

[a]AUC, area under the receiver operating characteristic curve.

FEIgG/SG (0.901) and FEα1m/SG (0.891); the histologic parameters showed AUC smaller than proteinuric parameters. FEIgG/SG showed the highest sensitivity (91%) and specificity (92%) for progression.

Progression Rate in All Patients and Univariate Survival Analysis for Progression

The functional outcome could be evaluated in 34 patients (follow up 60 ± 40 mo; range 2 to 135 mo); 11 (32%) patients progressed (ESRD $n = 8$ after 31 ± 32 mo; doubling sCr $n = 3$ after 46 ± 41 mo). The results of the univariate survival analysis comparing the low- and high-risk groups for each RF are reported in Table 5: sCr predicted progression in 5 *versus* 71% of patients ($P < 0.0001$). The single proteins divided for the percentage of SG showed a predictive value of progression higher than the absolute value of the same parameters: FEIgG/SG 5 *versus* 83% ($P < 0.0001$); FEIgG 5 *versus* 67% ($P = 0.0001$); FEα1m/SG 5 *versus* 77% ($P < 0.0001$); FEα1m 5 *versus* 71% ($P < 0.0001$); uα2m/g uCr/SG 12 *versus* 80% ($P = 0.0003$); uα2m/g uCr 5 *versus* 57% ($P = 0.025$). By contrast, 24hP/SG showed the same predictive value of 24hP: 11 *versus* 56% ($P = 0.010$) and 15 *versus* 57% ($P = 0.030$), respectively. All of the histologic parameters had lower predictive value. By multivariate analysis according to Cox model, only FEα1m/SG was an independent predictor of progression (hazard ratio 21.0; 95% confidence interval 1.5 to 282.0; $P = 0.02$).

Response to Therapy with Steroids and Cyclophosphamide

The outcomes of the 23 patients who were treated with steroids and cyclophosphamide were as follows: Progression $n = 8$ (35%; ESRD $n = 6$, doubling of sCr $n = 2$); no progression $n = 15$ (65%) (follow-up 55 ± 38 mo). The predictive value of all parameters is reported in Table 6. The nonprogressive patients showed at last observation (after 66 ± 38 mo) 65% reduction of 24hP (from 2.97 ± 3.49 to 0.61 ± 0.50 g/d; $P = 0.0009$), reduction of patients with 24hP ≥1 g from 73 to 7% ($P = 0.002$) and 10% sCr reduction (from 1.38 ± 0.54 to 1.21 ± 0.47 mg/dl; $P = 0.09$). The best predictor of progression was FEIgG/SG (0 *versus* 89%; $P < 0.0001$). Prediction of outcome was further increased by combination of FEIgG/SG with sCr, allowing more exact identification of the characteristics associated with treatment

Table 5. Univariate survival analysis: progression rate in low- and high-risk groups of sCr, proteinuric, and histologic parameters defined according to a cutoff with the highest sensitivity and specificity for progression (all patients independently from treatment)[a]

Risk Factors	Progression	*P*
sCr < *versus* ≥1.74 (20 *versus* 14)	5 *versus* 71%	<0.0001
FEIgG/SG < *versus* ≥0.00034 (22 *versus* 12)	5 *versus* 83%	<0.0001
FEα1m/SG < *versus* ≥0.04 (21 *versus* 13)	5 *versus* 77%	<0.0001
TID score < *versus* ≥3 (13 *versus* 21)	0 *versus* 52%	0.0059
GGS < *versus* ≥20% (18 *versus* 16)	11 *versus* 56%	0.0157
uα2m/g uCr/SG < *versus* ≥0.11 (24 *versus* 10)	12 *versus* 80%	0.0003
24hP/SG < *versus* ≥0.034 (24 *versus* 10)	11 *versus* 56%	0.0100
Cellular crescents < *versus* ≥17% (17 *versus* 17)	24 *versus* 41%	0.2580

[a]Numbers in parentheses are the number of patients of the low- and high-risk groups, respectively.

Table 6. Univariate survival analysis: progression rate in low- and high-risk groups of sCr, proteinuric, and histologic parameters in 23 patients treated with steroids and cyclophosphamide[a]

Risk Factors	Progression	*P*
sCr < *versus* ≥1.74 (12 *versus* 11)	0 *versus* 73%	<0.0001
FEIgG/SG < *versus* ≥0.00034 (14 *versus* 9)	0 *versus* 89%	<0.0001
FEIgG/SG + sCr (15 *versus* 8)[b]	0 *versus* 100%	<0.0001
FEα1m/SG < *versus* ≥0.04 (12 *versus* 11)	0 *versus* 73%	<0.0003
TID score < *versus* ≥3 (8 *versus* 15)	0 *versus* 53%	0.0210
GGS < *versus* ≥20% (12 *versus* 11)	8 *versus* 64%	0.0074
uα2m/g uCr/SG < *versus* ≥0.11 (15 *versus* 8)	7 *versus* 87%	0.0004
24hP/SG < *versus* ≥0.034 (9 *versus* 14)	0 *versus* 57%	0.0120
Cellular crescents < *versus* ≥17% (8 *versus* 15)	25 *versus* 40%	0.5960

[a]Numbers in parentheses are the number of patients of the low- and high-risk groups, respectively.
[b]Low-risk group: the two markers or only one below the cutoff; high-risk group: both markers above the cutoff.

responsiveness: When both markers are above the cutoff ($n = 8$; FEIgG/SG: ≥0.00034; sCr ≥ 1.74 mg/ml), the progression rate was 100%; when both markers or only one was below the cutoff ($n = 15$), the progression rate was 0% ($P < 0.0001$), notwithstanding four patients had baseline sCr above the cutoff (from 1.82 to 2.97 mg/dl) but FEIgG/SG below the cutoff; thus, also patients with advanced renal failure may be responsive to treatment when FEIgG/SG is below the cutoff. A formal interaction analysis was not possible because of lack of events (progression) in the low-risk group.

Discussion

cIgAN, characterized by extracapillary proliferation often associated with segmental glomerular necrosis, may be due to a pathogenetic mechanism different from what is universally accepted as prominent in IgAN—that is, the damaging effect of deposited macromolecular IgA1 on mesangial cells. It is hypothesized that a concomitant direct injury on the endothelial cells of the glomerular capillary wall (GCW), with its potential disruption, induces extracapillary proliferation (7).

Our data show that cIgAN is characterized by marked disruption of size selectivity of GCW, suggested by high urinary excretion of IgG and α2m (six- and 8.1-fold higher in patients with *versus* without cellular crescents). Moreover, cIgAN is characterized by a significantly higher rate of global glomerulosclerosis, larger extent of tubulointerstitial damage, and higher fractional excretion of α1m, a low molecular weight protein significantly correlated with the extent of TID in this study ($r = 0.664$, $P < 0.0001$) and in other glomerulonephritides (12,14). The high degree of correlation between TID score, FEIgG ($r = 0.725$), and uα2m/g uCr ($r = 0.497$) may suggest a pathogenetic link between excretion of high molecular weight proteins and the extent of TID as we showed in other glomerulonephritides in which selectivity index (15) or IgG excretion (12,14) was correlated with extent of TID.

The most powerful pathophysiologic mechanism of progression in cIgAN seems not to be the percentage of cellular crescents, as is suggested by lack of correlation with baseline sCr ($r = 0.208$) and lack of significant difference of progression rate in patients with crescents < *versus* ≥17% (24 *versus* 41%; $P = 0.25$). The assessment of the risk for progression of segmental cellular crescents on the basis of percentage of affected glomeruli may be rough because the overall extent of GCW covered by crescents and the overall severity of GCW damage cannot be quantitatively evaluated morphologically; this statement is suggested by the observation that patients with cellular crescents ≥17% and progressors have percentage of cellular crescents very similar to nonprogressors (34 ± 17 *versus* 29 ± 14; $P = 0.55$) but FEIgG/SG 16-fold higher than nonprogressors (0.00370 ± 0.00288 *versus* 0.00023 ± 0.00025, respectively; $P = 0.003$). On the basis of our data, the most powerful pathophysiologic mechanism associated with progression seems to be the extent of disruption of the glomerular barrier to proteins. FEIgG shows a high degree of correlation with baseline sCr ($r = 0.749$) and the highest prediction of progression when combined with the rate of nephron loss as in the new marker FEIgG/SG, which, taking into account not only the size selectivity alteration but also the degree of nephron loss, evaluates the effective IgG tubular load in surviving nephrons (progression in patients with FEIgG/SG < *versus* ≥0.00034: 5 *versus* 83%; $P < 0.0001$). Also FEα1m/SG has a high predictive value of progression (5 *versus* 77%; $P < 0.0001$) and is the only independent predictor of progression by multivariate analysis. We focused the attention on FEIgG for clinical and pathophysiologic reasons: FEIgG/SG by univariate analysis seems superior to FEα1m/SG in predicting progression in treated patients when considered both alone (89 *versus* 73%) and in combination with sCr (100 *versus* 80%), thereby allowing more exact identification of unresponsive patients. From the pathophysiologic point of view, one of the main events in glomerulonephritis is the alteration of glomerular barrier to proteins of which FEIgG is a reliable marker; the presence of high molecular weight proteins in glomerular filtrate upregulates chemokine expression and complement activation in tubular cells with induction of inflammatory cell infiltration in the interstitium and fibrogenesis (16–19); the increased excretion of α1m seems to be an epiphenomenon partially dependent on excretion of high molecular weight proteins. It is interesting that the predictive

value of 24hP and 24hP/SG are very similar (15 *versus* 57 and 11 *versus* 56%, respectively), suggesting that urinary excretion of high and low molecular weight proteins more exactly evaluates the severity of damage of GCW and tubular cells, thus better predicting progression. The value of FEIgG as predictor of progression and responsiveness to therapy is highlighted by our recent study of 140 patients with noncrescentic IgAN, 73 untreated and 67 treated with angiotensin-converting enzyme inhibitors (20), that showed that FEIgG $\geq$0.006 is the most powerful predictor of responsiveness to angiotensin-converting enzyme inhibitors (progression 20 *versus* 62% in treated *versus* untreated patients; $P = 0.0004$). We are aware that the evaluation of the percentage of surviving nephrons on the basis of the percentage of globally sclerotic glomeruli in biopsy specimens may be inaccurate, as a result of the limited number of glomeruli present in such specimens and the possibility that they are not necessarily representative of whole kidney; however, in our cohort of patients, the FEIgG, evaluated as a ratio with the percentage of SG, seemed to be a more accurate predictive marker of progression in comparison with the absolute value.

The best treatment of cIgAN is not well defined; few small observational studies have evaluated the efficacy of steroids and cyclophosphamide with variable results. Our study shows that in patients who were treated with steroids and cyclophosphamide, FEIgG/SG has the highest prediction of progression (0 *versus* 89%; $P < 0.0001$), prediction further increased by combination of FEIgG/SG and baseline sCr that allows identification of a high-risk group ($n = 8$ patients) with both markers above the cutoff (100% progression) and a low-risk group ($n = 15$ patients) with both markers or only one below the cutoff (0% progression, 65% lowering of 24hP, and 10% lowering of sCr at last observation). These results suggest that the combination of these two markers is a reliable predictor of responsiveness to therapy; thus, in patients with the characteristics selected in our study for immunosuppressive treatment (cellular crescents $\geq$10% and/or nephrotic proteinuria and/or rapidly progressive or chronic renal failure), a 6-mo treatment with intravenous followed by oral steroids and intravenous cyclophosphamide may prevent progression, reduce proteinuria, and improve or stabilize renal function in the low-risk patients with sCr or FEIgG/SG or both below their cutoff. Indication for the same treatment is doubtful in high-risk patients, because, lacking a group of untreated patients with similar baseline characteristics, it is not possible to exclude that treatment may delay progression.

Conclusions

cIgAN is characterized by severe disruption of glomerular barrier to proteins with marked urinary excretion of high molecular weight proteins. FEIgG is highly correlated with baseline sCr, percentage of GGS, extent of TID, and percentage of cellular crescents. FEIgG divided for the percentage of SG more exactly assesses the effective tubular load of IgG. This new marker (FEIgG/SG) is the most powerful predictor of progression in all patients and in patients who are treated with steroids and cyclophosphamide. Moreover, FEIgG/SG and sCr in combination allow identification of low- and high-risk groups with 100 *versus* 0% responsiveness to treatment, respectively. Low-risk patients should be treated with intravenous and oral steroids and intravenous cyclophosphamide for 6 mo because this treatment prevents progression.

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Disclosures

None.

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