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ORIGINAL ARTICLE

IgA nephropathy in Greece: data from the registry of the Hellenic Society of Nephrology

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Abstract

Background: Natural history, predisposing factors to an unfavourable outcome and the effect of various therapeutic regimens were evaluated in a cohort of 457 patients with immunoglobulin A nephropathy (IgAN) and follow-up of at least 12 months.

Methods: Patients with normal renal function and proteinuria <1 g/24 h as well as those with serum creatinine (SCr) >2.5 mg/dL and/or severe glomerulosclerosis received no treatment. Patients with normal or impaired renal function and proteinuria >1 g/24 h for >6 months received daily oral prednisolone or a 3-day course of intravenous (IV) methylprednisolone followed by oral prednisolone *per os* every other day or a combination of prednisolone and azathioprine. The clinical outcome was estimated using the primary endpoints of end-stage renal disease and/or doubling of baseline SCr.

Results: The overall 10-year renal survival was 90.8%, while end-stage renal disease and doubling of baseline SCr developed in 9.2% and 14.7% of patients, respectively. Risk factors related to the primary endpoints were elevated baseline SCr, arterial hypertension, persistent proteinuria >0.5 g/24 h and severity of tubulointerstial fibrosis. There was no difference in the clinical outcome of patients treated by the two regimens of corticosteroids; nevertheless, remission of proteinuria was more frequent in patients who received IV methylprednisolone (P = 0.000). The combination of prednisolone with azathioprine was not superior to IV methylprednisolone followed by oral prednisolone. Side effects related to immunossuppressive drugs were observed in 12.8% of patients.

Conclusion: The clinical outcome of patients with IgAN was related to the severity of clinical and histological involvement. The addition of azathioprine to a corticosteroid-based regimen for IgAN does not improve renal outcome.

Key words: IgA nephropathy, immunosuppressive drugs, chronic renal failure, prognosis, albuminuria

Introduction

Immunoglobulin A nephropathy (IgAN) represents the most commonly encountered primary glomerular disease in many developed countries. Episodes of macroscopic haematuria following viral infections of the upper respiratory tract and asymptomatic microscopic haematuria with proteinuria represent common manifestations of IgAN [1, 2]. Nephrotic syndrome and acute renal failure occur less frequently and histological involvement ranges from minimal mesangial proliferation to advanced glomerular and tubulointerstitial injury [3, 4]. Although the clinical course is typically benign, some patients develop renal failure [5, 6]. An unfavourable clinical outcome is related with arterial hypertension, impaired renal function, heavy proteinuria at presentation, severe histological involvement and persistent proteinuria during follow-up [7, 8]. MEST scores reflecting the severity of mesangial proliferation (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S) and tubular atrophy/interstitial fibrosis (T) are an independent factor predicting outcome [9], whereas the combination of MEST scores with clinical data at the time of biopsy provides earlier risk prediction [10].

Renin–angiotensin system blockers and immunosuppressive drugs have been used in patients with IgAN [11, 12]. Although patients with deteriorating renal function and severe histological involvement are treated aggressively, a recent randomized controlled trial demonstrated that the addition of immunosuppressive therapy to intensive supportive care did not significantly improve the outcome [13].

The purpose of this retrospective analysis was to estimate the natural history, predisposing factors to an unfavourable outcome and effect of various therapeutic regimens used in a large cohort of patients with IgAN from the registry of the Hellenic Society of Nephrology.

Materials and methods

Patients

Patients [$n = 457$ (303 males and 154 females), 41.3 ± 14.3 years of age] with biopsy-proven IgAN performed between 1990 and 2010 with follow-up of at least 12 months were included in the study. Of the 457 patients, 17 (3.7%) were <18 years old (mean age 15.2 ± 2.4 years). Patients with secondary causes of disease, such as Henoch–Schonlein purpura, systemic lupus erythaematosus and hepatic diseases, were excluded. The clinical, biochemical and histological features at diagnosis are summarized in Table 1. The mean follow-up period was 63.8 ± 37 months.

Therapeutic regimens

Conservative management

All patients with proteinuria >0.5 g/24 h received angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs). Patients who received only conservative management ($n = 262$) had the following characteristics normal renal function and proteinuria <1 g/24 h ($n = 225$) and baseline serum creatinine (SCr) >2.5 mg/dL and/or severe glomerulosclerosis (>30% totally sclerosed glomeruli) and tubulointerstitial fibrosis (T1/T2) ($n = 37$).

Immunosuppressive regimens

Corticosteroids alone or in combination with azathioprine or mycophenolate mofetil (MMF) were used in patients with normal or impaired renal function and persistent proteinuria >1 g/24 h for 6 months after initiation of ACEis or ARBs. The combination of corticosteroids with cyclophosphamide was restricted

Table 1. Clinical, biochemical and histological features of all patients (N = 457) at presentation

Gender (M/F), *n* (%)	303/154 (66.3/33.7)
Age (years)	41.29 ± 14.32
Baseline SCr (mg/dL)	1.48 ± 1.04
Urine protein (g/24 h)	1.7 ± 2.0
eGFR (MDRD; mL/min/1.73 m^2)	64.09 ± 30.7
Arterial hypertension (BP > 140/90 mmHg), *n* (%)	256 (56)
Microscopic haematuria, *n* (%)	403 (88.2)
Macroscopic haematuria, *n* (%)	142 (31.1)
Acute kidney injury, *n* (%)	30 (6.6)
Nephrotic range proteinuria, *n* (%)	56 (12.3)
Histological features (Oxford classification)	
MEST score, *n* (%)	198 (43.3)
Mesangial hypercellularity (M0/M1)	66/132
Endocapillary hypercellularity (E0/E1)	148/50
Segmental glomerulosclerosis (S0/S1)	90/108
Tubular atrophy/interstitial fibrosis (T0/T1/T2)	140/49/9
Haas classification	
Mesangial proliferation, *n* (%)	400 (87.5)
Mild	212
Moderate	149
Severe	39
Tubular atrophy, *n* (%)	447 (99.3)
Absent	174
Present	273
Interstitial inflammation/fibrosis, *n* (%)	338 (73.9)
Mild	97
Moderate	183
Severe	58
Vascular hyalinosis, *n* (%)	338 (73.9)
Absent	182
Present	156
Severity of mesangial IgA deposits, *n* (%)	334 (73)
Mild (+)	109
Moderate (++)	181
Severe (+++)	44

MDRD, Modification of Diet in Renal Disease.

to patients with a rapidly progressive course and/or crescents in the renal biopsy.

The immunosuppressive regimens used were the following.

Corticosteroids:

Oral prednisolone, 1 mg/kg body weight (BW)/day initially followed by gradual tapering for 12 months (*n* = 76).

Intravenous (IV) methylprednisolone, 1 g for 3 consecutive days on the first, third and fifth month of treatment followed by oral prednisolone 0.5 mg/kg BW every other day for 6 months (*n* = 57).

Corticosteroids and azathioprine:

Oral prednisolone, 1 mg/kg BW/day initially followed by gradual tapering with azathioprine at 2 mg/kg BW/day initially reduced to 50 mg/day by the end of the first year and continued for 6 additional months (*n* = 32).

The clinical, biochemical and histological features of patients treated by these regimens are presented in Table 2.

Corticosteroids and MMF:

Oral prednisolone, 1 mg/kg BW/day initially followed by gradual tapering with MMF, 2 g/day initially, reduced to 1 g/day by the end of the first year and continued for 6 additional months (*n* = 9).

Corticosteroids and cyclophosphamide:

IV methylprednisolone pulse for 3 days followed by prednisolone 0.5 mg/kg BW/day and IV cyclophosphamide 0.5 g/m^2/month for 6 months (*n* = 21). Cyclophosphamide was then replaced by azathioprine (50–100 mg/day) for 12 additional months.

Follow-up and definitions

BW, blood pressure (BP), biochemical profile and 24-h urinary protein was recorded regularly during follow-up. All patients received ACEis or ARBs with a target blood pressure <130/80 mm Hg.

The clinical outcome was estimated using the primary endpoints of end-stage renal disease (ESRD) and/or doubling of baseline SCr. Remission of proteinuria was defined as a

Table 2. Clinical and histological features at presentation of patients treated by oral prednisolone/daily, IV methylprednisolone and then oral prednisolone on alternate days and combination of prednisolone and azathioprine

	Oral prednisolone daily	IV methyprednisolone and prednisolone on alternate days	Prednisolone plus azathioprine	P-value
Clinical features				
Number of patients	76	57	32	
Gender (M/F)	50/26	43/14	25/7	Non significant (NS)
Age (years)	39.4 ± 15.3	42.36 ± 13.25	44.47 ± 10.68	NS
Baseline SCr (mg/dL)	1.87 ± 1.7	1.37 ± 0.64	1.69 ± 0.78	NS
Urine protein (g/24 h)	2.4 ± 2.8	2.9± 2.3	2.4 ± 1.3	NS
eGFR (MDRD; mL/min/1.73 m^2)	59.2 ± 34.4	67.7 ± 31.5	50.7 ± 28.2	NS
Arterial hypertension (BP > 140/90 mmHg), *n*	10	4	3	NS
Microscopic haematuria, *n*	12	3	3	NS
Macrohaematuria, *n*	2	1	0	NS
Nephrotic range proteinuria, *n*	3	1	1	NS
Histological characteristics (Oxford classification)				
MEST score, *n*	29	30	17	
Mesangial proliferation (M0/M1)	7/22	14/16	6/11	NS
Endocapillary hypercellularity (E0/E1)	21/8	22/8	9/8	NS
Segmental glomerulosclerosis (S0/S1)	10/19	16/14	5/12	NS
Tubular atrophy/interstitial fibrosis (T0/T1/T2)	16/8/5	18/10/1	9/8/0	NS

MDRD, Modification of Diet in Renal Disease.

reduction of 24-h urinary protein to <0.5 g/24 h, which was considered as a secondary endpoint.

Conventional pathology and grading of histopathological lesions

The diagnosis of IgAN was made by appropriate biopsy specimens (>10 glomeruli) exhibiting mesangial proliferation on light microscopy with IgA deposition on immunofluorescence [4]. The severity of histological involvement was evaluated from Masson's trichrome–stained sections using a semi-quantitative method and graded as mild, moderate and severe. The severity of IgA deposition on immunofluorescence was expressed as mild (+), moderate (++) and severe (+++). The Oxford classification [mesangial hypercellularity, endocapillary hypercellularity, segmental glomerulosclerosis and tubular atrophy/interstitial fibrosis (MEST) score] was available in 198 of 457 patients (43.3%). According to this classification, the presence of mild or severe mesangial proliferation is classified as M0 and M1, the absence or presence of endocapillary hypercellularity as E0 and E1 and segmental glomerulosclerosis as S0 and S1. Tubulointerstitial fibrosis was classified as T0, T1 and T2 according to its extension to 0–25%, 25–50% or >50% on the kidney biopsy surface, respectively [9].

Statistical analysis

SPSS software (SPSS Statistics for Windows, Version 22.0; IBM, Armonk, NY, USA) was used for analysis. A P-value of 0.05 was considered statistically significant. Data are presented as the mean ± standard deviation (SD) (continuous variables) and as counts, percentages and odds ratios with 95% confidence intervals (CIs) (categorical variables). The χ^2 test was used to determine significant differences between expected and observed frequencies in categorical variables. Kaplan–Meier and Cox proportional hazards models were used to test the association between any factor, covariate and the three endpoints. Survival analysis (expressed by endpoints) was performed using the log-rank test. A logistic regression model that included two stratification factors (proteinuria remission and time to remission) was fitted to the data of endpoints.

Results

Clinical presentation

Arterial hypertension (BP > 140/90 mmHg) at presentation was observed in 256 patients (56.3%), microscopic haematuria in 403 (88%) and macroscopic haematuria in 142 of 457 patients (31%). Most patients with macroscopic haematuria had no proteinuria patients (88%). No substantial proteinuria (<0.5 g/24 h) was observed in 114 patients (24.9%), nephrotic range proteinuria in 56 (12.3%) and acute renal injury in 30 (6.6%) (Table 1).

Histological findings at diagnosis

In patients with a MEST score ($n = 198$), mesangial proliferation was classified as M0/M1 in 66 and 132 (33.9% versus 66.1%), endothelial proliferation as E0/E1 in 148 and 50 (74.7% versus 25.3%), segmental sclerosis as S0/S1 in 90 and 108 (45.5% versus 54.5%) and tubulointerstitial fibrosis as T0/T1/T2 in 140, 49 and 9 patients (70.7%, 24.7% and 4.5%), respectively (Table 1).

Estimation of the severity of IgA deposition was available in 334 patients. The severity of IgA deposition was expressed as mild in 109 patients (32.7%), moderate in 181 (54.1%) and severe in 44 (13.2%) (Table 1).

Clinical outcome

The overall 10-year renal survival was 90.8%. The primary endpoints of ESRD and doubling of baseline SCr were noted in 42 (9.2%) and 67 (14.7%) patients, respectively (Figure 1A and B). The mean time for doubling of baseline SCr was 109.5 ± 1.4 months.

Of 42 patients who developed ESRD, 18 received no immunosuppressive treatment, 14 received oral prednisolone daily, 4 received IV methylprednisolone initially followed by oral prednisolone, 3 received prednisolone and azathioprine, 2 received prednisolone and cyclophosphamide and 1 received prednisolone and MMF.

Risk factors related to the development of ESRD and doubling of baseline SCr

The risk factors related to the development of both endpoints were as follows (Table 3) elevated baseline SCr (2.41 ± 1.3 mg/dL and 1.96 ±1.2 mg/dL versus 1.38 ±0.9 mg/dL in patients with preserved renal function; P = 0.000); arterial hypertension at diagnosis (P = 0.001); persistent proteinuria >0.5 g/24 h over the follow-up period (P = 0.002 and 0.014, respectively); the presence of segmental glomerulosclerosis (S1) (P = 0.009 and 0.003, respectively) (Figure 2A and B) and the severity of tubular atrophy/interstitial fibrosis (T1 and T2) (P = 0.000 and 0.001, respectively) (Figure 2C and D).

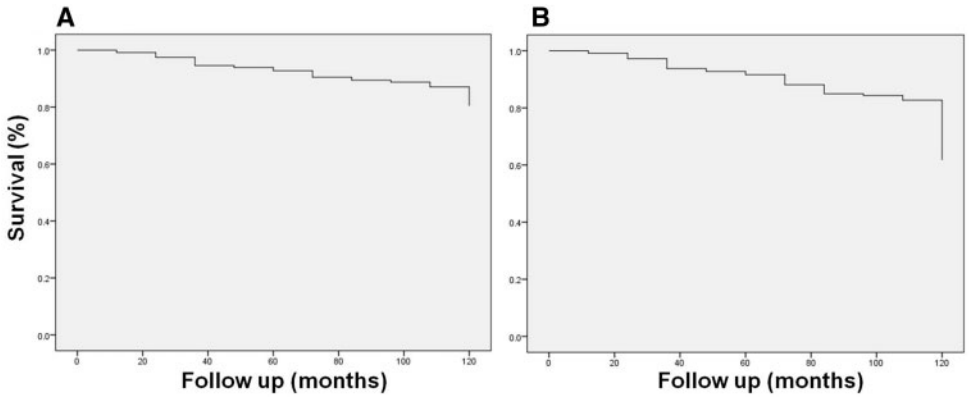

Fig. 1. (**A**) Cumulative renal survival free from the endpoints of ESRD) and (**B**) doubling of baseline SCr in all patients.

Table 3. Parameters related to the development of primary endpoints (after 10 years of observation)

	ESRD			Doubling of serum baseline creatinine		
	Mean ± SD or *n* (%)	P-value	HR (95% CI)	Mean ± SD or *n* (%)	P-value	HR (95% CI)
Baseline SCr (mg/dL)	2.41 ± 1.3	0.000	0.118 (0.052–0.265)	1.96 ± 1.2	0.000	0.387 (0.238–0.631)
Arterial hypertension at diagnosis, *n* (%)	35 (87.5)	0.000	0.173 (0.068–0.440)	50 (72.5)	0.001	0.397 (0.226–0.697)
Persistent urine protein >0.5 g/24 h over the follow-up period, *n* (%)	37 (92.5)	0.002	0.143 (0.034–0.591)	58 (84.1)	0.014	0.424 (0.210–0.858)
Presence of segmental glomerulosclerosis (S1, Oxford classification), *n* (%)	19 (47.5)	0.009	0.263 (0.089–0.777)	25 (36.2)	0.003	0.284 (0.116–0.692)
Presence of tubular atrophy/interstitial fibrosis (T1/T2, Oxford classification), *n* (%)	15 (37.5)	0.000	0.106 (T1) (0.035–0.339) 0.525 (T2) (0.176–1.564)	17 (24.6)	0.001	0.224 (T1) (0.085–0.589) 0.710 (T2) (0.251–2.002)

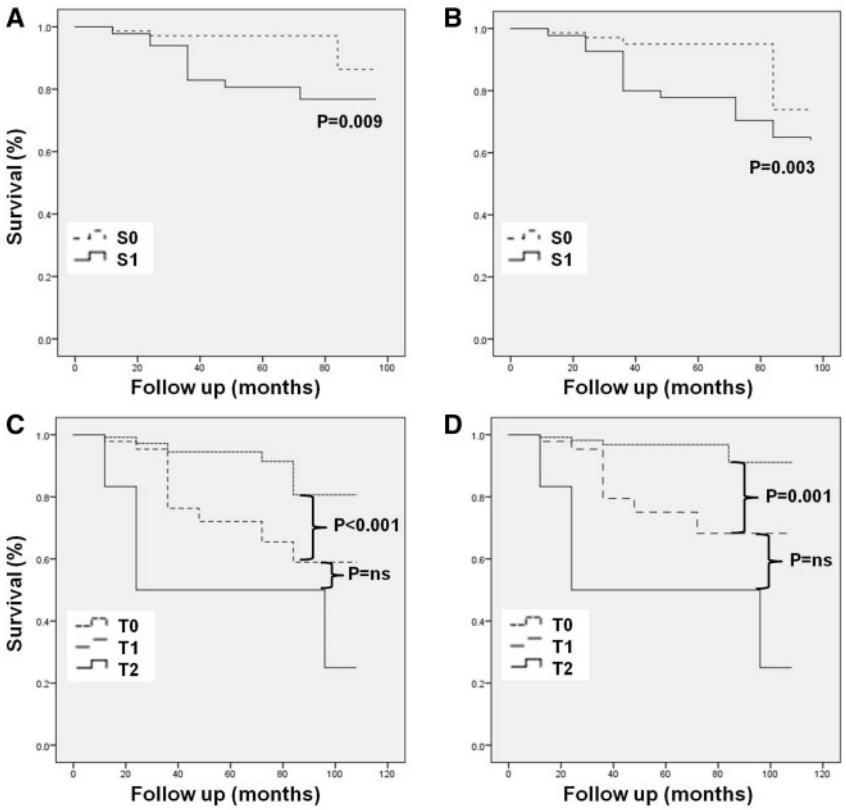

Fig. 2. MEST classification and primary endpoints. (**A**) Segmental glomerulosclerosis (S0/S1) in the kidney biopsy and survival free from ESRD or (**B**) doubling of baseline SCr. (**C**) Tubular atrophy/interstitial fibrosis (T0/T1/T2) in the kidney biopsy and survival free from ESRD or (**D**) doubling of baseline SCr.

Remission of proteinuria

Of 343 patients with proteinuria >0.5 g/24 h, 217 (63.3%) exhibited a reduction of proteinuria to <0.5 g/24 h with either conservative or immunosuppressive treatment. The 10-year renal survival free from ESRD rate was 99% in patients with no substantial proteinuria, 96.3% in those with remission and 75.4% in patients with persistent proteinuria ($P < 0.001$) (Figure 3). Once remission of proteinuria was achieved, the rate of survival free from ESRD was similar in patients who received immunosuppressive drugs or conservative management.

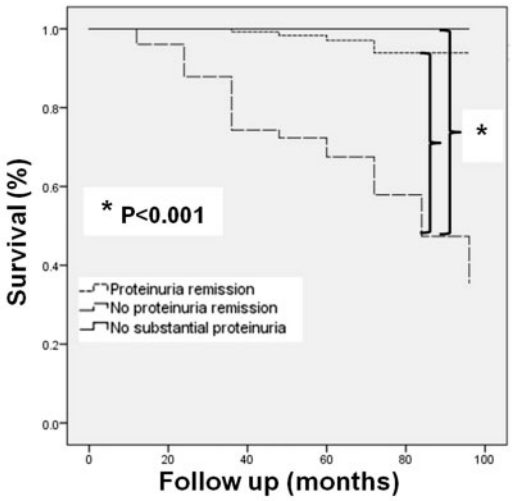

Fig. 3. Survival free from the endpoint of ESRD in patients with no substantial proteinuria, patients with remission and patients with no remission of proteinuria.

Persistent proteinuria (>0.5 g/24 h) was related to endocapillary hypercellularity (E1), tubular atrophy/interstitial fibrosis (T1/T2) (P = 0.020 and 0.006) and the severity of mesangial IgA deposition (P = 0.001).

Therapeutic regimens and clinical course

Conservative management

Of 262 patients who received conservative management, 18 (6.9%) progressed to ESRD and 35 (13.4%) doubled their baseline SCr. The main differences between patients who reached the primary endpoints or preserved renal function were the degree of renal function and severity of proteinuria. SCr, estimated glomerular filtration rate (eGFR) and 24-h urine protein at diagnosis in patients who reached ESRD, doubled baseline SCr or preserved their renal function were 1.76 ± 0.63 mg/dL, 47.08 ± 24.8 mL/min/1.73 m^2 and 1.8 ± 0.9 g/24 h; 1.48 ± 0.62 mg/dL, 59.5 ± 28.6 mL/min/1.73 m^2 and 1.4 ± 0.6 g/24 h and 1.23 ± 0.69 mg/dL, 68.9 ± 28.3 mL/min/1.73 m^2 and 1.1 ± 1.1 g/24 h, respectively. Of 37 patients with baseline SCr >2.5 mg/dL and/or severe glomerulosclerosis, 13 reached ESRD (35%). Of 225 patients with normal renal function and proteinuria <1 g/24 h, 5 developed ESRD (2.2%).

Corticosteroids

Oral corticosteroids daily versus IV pulse followed by oral corticosteroids every other day. The clinical and histological features of patients treated with oral prednisolone daily (n = 76) or by IV methylprednisolone for 3 consecutive days on the first, third and fifth month of treatment followed by oral prednisolone every other day (n = 57) were comparable (Table 2).

Of 76 patients treated with oral prednisolone, 14 (18.4%) reached ESRD and 15 (19.7%) doubled baseline SCr. Of 57 patients treated with IV methylprednisolone, 4 (7%) reached ESRD and 9 (15.8%) doubled baseline SCr. No significant differences were found in reaching ESRD or doubling of SCr between patients in these two different treatment groups. Reduction of proteinuria to <0.5 g/24 h was achieved in 35 patients (46%) in the former group and in 41 patients (72%) in the latter group (P = 0.000).

Corticosteroids and azathioprine. The clinical and histological features of patients treated with prednisolone and azathioprine (n = 32) were comparable to those treated with corticosteroids alone (Table 2). Of these 32 patients, 3 (9.4%) reached ERSD and 5 (15.6%) doubled baseline SCr. Remission of proteinuria to <0.5 g/24 h was observed in 17 patients (53%).

No significant difference was observed in the development of primary endpoints between patients treated with prednisolone and azathioprine and those treated with oral prednisolone daily or IV methylprednisolone. An increased proteinuria remission rate was observed in patients treated with prednisolone and azathioprine compared with those treated with oral prednisolone daily (P = 0.037).

Corticosteroids and MMF. A combination of prednisolone and MMF was used in nine patients (baseline SCr 1.74±0.84 mg/dL, eGFR 51.5 ± 26.7 mL/min/1.73 m^2, urine protein 3.9 ± 4.9 g/24 h). Of these patients, one doubled baseline SCr and reached ESRD and six reduced proteinuria to <0.5 g/24 h.

Corticosteroids and cyclophosphamide. IV methylprednisolone pulses for 3 days followed by oral prednisolone and IV cyclophosphamide every month for 6 months was administered to 21 patients with a rapidly progressive course and/or cellular crescents in >40% of glomeruli in the renal biopsy (baseline SCr 2.64 ± 1.43 mg/dL, eGFR 37.7 ± 27.8 mL/min/1.73 m^2, urine protein 2.9 ± 2.8 g/24 h). Of 21 patients, 2 doubled baseline SCr and reached ESRD and 14 reduced proteinuria to <0.5 g/24 h.

Side effects of treatment

Side effects related to immunosuppressive drugs were observed in 25 of 195 treated patients (12.8%). Adverse events related to corticosteroids included osteonecrosis and/or osteopenia in three patients, myopathy in four, glaucoma in two, cushingoid symptoms in six and deterioration of bipolar disease in one. Among patients who received azathioprine, gastrointestinal symptoms were observed in two, elevated liver enzymes in two and leucopenia in one. Among patients who received MMF, gastrointestinal symptoms were observed in one, leucopenia in one and osteomyelitis in one.

Discussion

The natural history of IgAN, the parameters related to an unfavourable outcome and the effects of treatment with various immunosuppressive drugs were estimated in a retrospective analysis of a large cohort from the registry of the Hellenic Society of Nephrology.

Macroscopic haematuria, a common manifestation of the disease, was frequently observed, whereas nephrotic range proteinuria and acute kidney injury were confirmed as rare manifestations. The 10-year renal survival was 90.8%, which is similar to that reported in the literature [5, 6].

Recent data from the European Validation Study of the Oxford Classification of IgA Nephropathy (VALIGA) study demonstrated that time averaged proteinuria <0.5 g/day was a significant marker of better outcome [14]. Elevated baseline SCr, arterial hypertension, persistent proteinuria >0.5 g/24 h, presence of segmental glomerulosclerosis and severity of tubulointerstitial fibrosis were related to the development of ESRD and doubling of baseline SCr in our cohort. The presence of crescents in the biopsy was not related to a more rapid decline of renal function in some studies [15], a finding that was also confirmed in this study in patients with cellular crescents in >40% of the total number of glomeruli in the kidney biopsy, probably due to the aggressive treatment administered to these patients. Of note, the rate of survival free from ESRD was not

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related to conservative or immunosuppressive treatment, but only to proteinuria remission. The degree of proteinuria at diagnosis, presence of endocapillary hypercellularity, tubulointerstitial fibrosis and severity of IgA deposition correlated with persistent proteinuria. The correlation of mesangial proliferation and endocapillary hypercellularity with proteinuria has been recognized in VALIGA [14].

Patients with normal renal function and a lack of proteinuria have a favourable outcome, whereas patients with baseline SCr >2.5 mg/dL and severe glomerulosclerosis are not good candidates for immunosuppressive treatment because they have reached the 'point of no return' [16]. Of 42 patients who reached ESRD, 18 received no immunosuppressive drugs, including 13 patients from the subgroup of 37 patients with baseline SCr >2.5 mg/dL and/or severe glomerulosclerosis. The remaining 5 patients were from the subgroup of 225 patients with normal renal function and proteinuria <1 g/24 h. These patients had inadequate control of their BP over a long period of time.

Administration of a 6-month course of corticosteroids (1 g IV methylprednisolone for 3 consecutive days every other month and 0.5 mg/kg BW oral prednisolone every other day) in patients with proteinuria (1–3.5 g/24 h) and well-preserved renal function (SCr < 1.5 mg/dL) was more effective than supportive treatment in a randomized trial over a 10-year follow-up [17]. A beneficial effect with low-dose prednisolone was also observed in a controlled prospective trial in patients with moderate histological changes [18]. These results were confirmed in a meta-analysis of all randomized prospective trials [19]. Recent studies demonstrate that treatment with corticosteroids in combination with ACEis is more effective than ACEis alone in patients with proteinuria [20, 21]. The beneficial effect of corticosteroids in addition to renin–angiotensin system blockade was also confirmed in VALIGA and other studies [22, 23]. Although a considerable amount of data on the use of two regimens of corticosteroids in patients with IgAN has been reported, no comparison between these regimens has been reported to date. In this study, both regimens were used in patients with similar clinical and histological features. Although there was no significant difference in the development of primary endpoints, a significantly higher remission rate of proteinuria to <0.5 g/24 h was noted with IV methylprednisolone followed by oral prednisolone every other day (remission rate 72% versus 46%: $P = 0.000$).

Corticosteroids in combination with azathioprine offers a beneficial effect in patients with heavy proteinuria (>3 g/24 h) and impaired renal function in a retrospective study with 10-year follow-up [24]. Others report that IgAN patients who do not respond to steroids might respond to a combination of steroids and azathioprine [25]. However, in a randomized prospective trial, the effect of a 6-month course of corticosteroids and azathioprine was not superior to a 6-month course of corticosteroids alone [26]. The same authors reported that the addition of azathioprine may be slightly more effective than corticosteroids alone in patients with chronic renal insufficiency and proteinuria [27], but it can increase the risk of side effects [28]. In this study, no significant difference in the development of primary endpoints was observed between patients treated with prednisolone and azathioprine and those treated with corticosteroids alone. However, an increased remission rate of proteinuria was noted among patients treated with prednisolone and azathioprine and patients treated with IV methylprednisolone compared with patients treated with oral prednisolone daily ($P = 0.037$).

MMF has also been used in patients with IgAN, with conflicting results [29–34]. No conclusions can be drawn from our study given the limited number of patients treated with MMF. Cytotoxic drugs have been used in patients with rapidly progressive IgAN with good results [35, 36]. In a randomized prospective trial, patients with progressive disease and proteinuria were allocated to either prednisolone (40 mg/day) and cyclophosphamide (1.5 mg/kg BW/day for 3 months) followed by azathioprine for 2 years or conservative management [37]. A better renal survival rate after 5 years of follow-up was observed in patients treated with immunosuppressive drugs. The beneficial effects of corticosteroids and cyclophosphamide have also been reported in patients with aggressive disease and proteinuria [38, 39]. In this study, a combination of corticosteroids and IV cyclophosphamide every month for 6 months was effective in patients with a rapidly progressive course. However, this combination should be used with great caution given the long-term risk of the development of malignancies [40]. In a recent randomized controlled trial, the addition of immunosuppressive therapy to intensive supportive care in patients with high-risk IgAN was estimated over a 3-year follow-up period [13]. During a 6-month run-in phase, all patients received comprehensive supportive care with blockers of the renin–angiotensin system to reduce proteinuria to <0.75 g/day. High-risk patients who had persistent proteinuria entered a 3-year study phase and were randomly assigned to supportive care or supportive care plus immunosuppressive therapy with corticosteroids or a combination of corticosteroids with cyclophosphamide as previously reported [17, 39]. According to the results, the addition of immunosuppressive therapy to intensive supportive care did not significantly improve outcome and was followed by more adverse effects.

The main limitation of our study is that this is a retrospective analysis including patients from many centres with possible different therapeutic principles. However, as was confirmed at the end, the general recommendations have been adopted by all centres.

In conclusion, the choice of the therapeutic regimen should be based on the severity of clinical and histological involvement. A combination of conservative management with immunosuppressive drugs seems to be a reasonable approach in patients with persistent proteinuria and severe histological involvement to delay progression of IgAN.

Conflict of interest statement

None declared.

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