



# TREATMENT OF IGA NEPHROPATHY OF ADULTS PRESENTED BY NEPHROTIC SYNDROME

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## ABSTRACT

The aim of this retrospective study was to evaluate the results of the immunosuppressive regiment in managing of IgA nephropathy associated with primary nephrotic syndrome at the Nephrology Clinic, University of Sarajevo Clinics Centre in period of 1997-2007.

We studied 19 patients (4 women and 15 men) with idiopathic nephrotic syndrome, where pathomorphologic changes of IgA nephropathy were proved by kidney biopsy. The levels of diuresis, proteinuria, albuminemia, lipidemia and kidney function, as measure of efficiency of used therapy, were monitored.

The IgA nephropathy present with the nephrotic syndrome was shown in 15,8 % (19) patients underwent renal biopsy due to primary nephrotic syndrome in the period of observation. The average age of patients with IgA nephropathy was 34,9 ± 14,1 years. Eight patients from this group were treated with corticosteroid therapy (1-1,5 mg/kg of body weight for 4 weeks, followed by 0,5 mg/ kg of body weight until therapeutic response was achieved, and finally gradual exclusion of therapy after eight weeks in responsive patients), 6 patients with corticosteroids and bolus cyclophosphamide (10 -15 mg/kg BW), and in 5/19 patients cyclosporine therapy was used (3 mg/kg BW). Complete remission of nephrotic syndrome was achieved in 42,1% of the patients. In conclusion, in adults patients with primary nephrotic syndrome associated with IgA nephropathy, used immunosuppressive therapy resulted in a high percentage of achieved remissions.

KEY WORDS: IgA nephropathy, nephrotic syndrome, treatment, outcome

## INTRODUCTION

IgA nephropathy is the most common glomerular disease which covers 25-50% of all types of glomerulonephritis (1,2). It is characterized by the deposition of immune complexes in mesangial areas, predominantly IgA. Although the most common finding of IgA nephropathy on renal biopsy is focal mesangioproliferative glomerulonephritis, IgA nephropathy can be presented by various histological appearances, ranging from minimal lesions to diffuse proliferative and crescent glomerulonephritis. For a very long time this disease was considered to be benign, however, many researchers have shown that chronic renal failure occurs in 15 % of the cases within 10 years, while 25-50% of the cases this disease progress to end-stage renal disease within 20 years (3). Hypertension, severe proteinuria and especially clinical picture of nephrotic syndrome (NS) have shown to be negative prognostic indicators.

As the pathogenesis of IgA nephropathy is obscure, specific treatment for this disease still doesn't exist. Thanks to many researchers and analyses, nowadays we have more or less accepted principles of treatment for IgA nephropathy presented by nephrotic syndrome. The aim of this paper was to evaluate the effects of applicable therapy protocols in patients with primary nephrotic syndrome at the Nephrology Clinic University of Sarajevo Clinics Centre (CCU) from 1997 to 2007, where IgA nephropathy was proven by renal biopsy. Average observation period for each patient was one year.

## SUBJECTS AND METHODS

The retrospective analysis covered 19 patients (15 male and 4 female), of average age  $34,9 \pm 14,1$ , with pathohistologically proved IgA nephropathy during the period 1997-2007 at the Nephrology Clinic CCU in Sarajevo. More than a half of the patients with IgA nephropathy (52,63%) were less than 30 years old. All patients fulfilled the basic criteria for diagnosing primary NS. Previously, all secondary causes of nephrotic syndrome where IgA deposits in mesangium appeared as a secondary reaction on the basic pathohistological state (Purpura Henoch-Schonlein, Lupus erythematosus systemicus, Hepatitis chr, Nephropathia diabetica, etc), were excluded through relevant clinical investigations. Kidney biopsy was performed under ultrasound control by the usage of biopsy gun with 29-cm-long needles of 18G (1,2 mm), during which two cylindrical samples of kidney tissue were taken. Pathohistologic analysis included the

light and immunofluorescent analyses of kidney tissue. Within this patomorphologic entity, patients were divided based on the therapy protocol used. The outcome of the used treatment was followed by monitoring the level of total serum proteins, proteinuria and creatinine clearance. Laboratory tests were controlled in intervals no longer than one month, depending on the pace of treatment. The outcome of the disease was defined as complete remission, partial remission or persistence of NS. Complete remission of NS was defined as proteinuria less than 0,25 g/day in three consecutive measuring, partial remission of NS as proteinuria between 0,25 g/day and 3,5 g/day in three consecutive measuring, while persistence of NS was defined as proteinuria more than 3,5 g/day in three consecutive measuring. The test results were statistically processes using descriptive statistics and Student-t test, with the acceptance of statistical significance at the level  $p < 0,05$ . The results are shown in graphic and tabular form.

## RESULTS

In the period 1997-2007, IgA nephropathy was pathohistologically proven in 15,8% of the cases with primary nephrotic syndrome. Among the observed patients who had IgA nephropathy and nephrotic syndrome, diffuse proliferation of mesangium with more than 50% of hypercellular glomeruli were found in 76,6% of the cases, which classified them in pathohistological subclass IV IgA nephropathy, while 23,4% of the cases showed histological appearance of subclass III (focal proliferative glomerulonephritis). Crescent formations were seen in 20% of the cases with IgA nephropathy. The deposits of IgA found in mesangium of glomeruli, ranging between 0 and 4+, were in 61,5% of the cases 2+ intensity, and in 23% of the cases 4+ intensity. Interstitial lesions were found in 38,5% of the cases. Table 1 shows the number of patients with IgA nephropathy associated with nephrotic syndrome according to the therapy protocols applied. Corticosteroids (initial dosage 1-1,5 mg/kg BW/4 weeks, then dosage reduction to 0,5 mg/kg BW until the achievement of therapeutic response, followed by gradual termination of therapy 8 weeks after achieved the therapeutic response) were the basis of therapy protocol for patients monitored. The patients with IgA nephropathy associated with nephrotic syndrome, resistant to corticosteroids only, were treated with a combination of corticosteroids and pulse therapy of cyclophosphamide (10-15 mg/kg BW), or with cyclosporine (3 mg/kg BW, level of cyclosporine in blood app. 100 ng/ml).

Pathohistologic change	IgA Nephropathy		
	Corticosteroids + bolus cyclophosphamide	Cyclosporine	Corticosteroids
Type of treatment			
Number of patients	6	5	8

TABLE 1. Treatment of primary nephrotic syndrome of IgA

Table 2 shows the treatment results of patients (19) with IgA nephropathy and nephrotic syndrome in relation to quantitative values of proteinuria and serum proteins before and after the treatment. Complete remission of nephrotic syndrome was achieved in 42,1% of the patients (8). Only corticosteroids were used with 4 patients, 2 patients were treated with pulse therapy of cyclophosphamide with corticosteroids and 2 patients were treated with cyclosporine. Partial remission of NS was achieved in 42,1% of the cases. The remaining 15,8% of the patients also treated, still showed the signs of persistent nephrotic syndrome.

	Proteinuria (g/L)		Serum proteins (g/L)	
	Before the therapy	After the therapy	Before the therapy	After the therapy
Complete remission (42,1%)	4,93±2,49	0,24±0,6	56,54±8,5	70,0±5,74
p values	<0,001	<0,001		
Partial remission (42,1%)	5,44±2,89	2,09±0,74	60,2±9,57	63,4±4,61
p values	<0,05	<0,005		
Persistent NS (15,8%)	6,2±2,0	7,4±2,93	44,33±8,1	42,0±1,0
p values	0,58	0,584		

TABLE 2. Therapy effects of IgA nephropathy with nephrotic syndrome

The outcome of the kidney disease in relation to the therapeutically model used is shown in Table 3.

Pathohistologic change	IgA Nephropathy		
	Corticosteroids + bolus cyclophosphamide	Cyclosporine	Corticosteroids
Type of treatment			
Number of patients	6	5	8
Complete remission	2	2	4
Partial remission	3	2	3
Persistent NS	1	1	1

TABLE 3. Outcome of disease and type of treatment

The therapy protocols applied were not followed by the deterioration of kidney function. Creatinine clearance did not change significantly in the period monitored (Table 4).

Pathohistologic category	Creatinine clearance (ml/min)	
	Before the therapy	After the therapy
IgA GN (X±δ)	98,07±38,25	88,74±19,13
p values	0,574	

TABLE 4. Therapy effects on creatinine clearance

## DISCUSSION

Histological appearance of IgA nephropathy can range from minimal lesions to diffuse proliferative crescent glomerulonephritis, which was used by Lee and colleagues (4) to make the pattern of histological classification of the disease in five subclasses. Many studies have confirmed that IgA nephropathy histological features significantly correlate with the clinical outcome of disease (5).

IgA nephropathy was confirmed in 15,8% our patients with primary nephrotic syndrome, with more frequent occurrences of this disease in men (67,77%) than in women (30,23%). Most of our patients had histological changes belonging to subclass IV. Immunofluorescent microscopy showed mesangial hypercellularity with different degrees of mesangial matrix expansion, as well as mesangial IgA deposits with intensity ranging from 2+ to 4+.

Although some authors (6) have confirmed that the most common appearance of nephrotic syndrome is within focal segmental glomerulosclerosis as the subclass II of IgA nephropathy, further findings showed that high proteinuria appear in higher subclasses of histological changes (II to V), as observed in our patients.

IgA nephropathy can adversely progress and hasn't an established therapy. In 1999 Nolin and Courteau (7) suggested, based on results of small randomized controlled studies, the treatment of this form of glomerulonephritis by corticosteroids. A secondary analysis of a multicenter, randomized, controlled trial of 86 adult IgA nephropathy patients (8) was shown that ten-year renal survival was significantly better in the group patients who were receiving intravenous methylprednisolone plus oral prednisolone for six months that in the control group (97% versus 53%, p=0,0003). However, several studies emphasized need to use cytotoxic drugs in patients with high risk of progressing IgA nephropathy. In 2002, Ballardie and Roberts (9) published the results of a controlled single-centre study of IgA nephropathy treatment with progressive impairment of kidney function. A significantly better preservation of renal function was observed during the five

years follow-up, as well as the reduction of proteinuria during 12 months in a group of patients treated with corticosteroids and cytotoxic drugs compared to the control group, treated with supportive therapy only.

We used three types of treatment strategy with our patients. Complete remission was achieved in 8 patients (42,1%) Only corticosteroids were used with 4 patients, 2 patients were treated with pulse therapy of cyclophosphamide plus corticosteroids and 2 patients were treated with cyclosporine. Partial remission of NS was achieved in 8 patients (42,1%) treated by one of the mentioned strategies, and three patients (15,79%) were resistant to therapy applied. Most of complete and partial remissions achieved were the result of applied corticosteroids ther-

apy. Similar results have been reported by other authors.

Katafuchi (10) recommends the use of high doses of corticosteroids as treatment strategy of IgA nephropathy associate with proteinuria more than 3,5 g/day, while others recommend the combination of pulse doses of methylprednisolone and cyclophosphamide i.v. every month, during six months (11). There are some opinions that IgA nephropathy associated with NS is often steroid resistant, but that it can respond to cyclosporine treatment (12), which was confirmed in several of our patients. Recently studies suggest that treatment of IgA nephropathy with new immunosuppressive drugs like mycophenolate mofetil may be effective in achieving complete or partial remission of NS in this glomerular disease (13).

## CONCLUSION

- The greatest number of patients with nephrotic syndrome analyzed had the histological appearance of IgA nephropathy, subclasses IV
- The use of corticosteroids as a treatment strategy of IgA nephropathy in an initial dose of 1-1.5 mg/kg BW resulted in the highest number of complete and partial remissions of nephrotic syndrome achieved, along with preserved renal function.
- A good treatment outcome can be achieved in patients with IgA nephropathy associated with nephrotic syndrome, resistant to corticosteroid monotherapy, by adding pulse doses of cyclophosphamide or cyclosporine monotherapy only.

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