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This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/104061> since

Published version:

DOI:10.5301/JN.2011.8452

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UNIVERSITÀ DEGLI STUDI DI TORINO

This is an author version of the contribution published on:

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JN. JOURNAL OF NEPHROLOGY (2011) 25

DOI: 10.5301/JN.2011.8452

The definitive version is available at:

<http://www.jnephrol.com/Attach.action?cmd=Download&uid=AFBC5F9E-9101-485C-8F2>

Long-term effects of methylprednisolone pulses and mycophenolate mofetil in IgA nephropathy patients at risk of progression.

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Conflict of interest statement: None.

Abstract

Background: IgA nephropathy (IgAN) is a microcosm of glomerular lesions. Some histologic lesions are irreversible and progress toward obliteration of glomerular capillaries. Others are acute inflammatory processes potentially susceptible to reversal by means of immunosuppressive therapies. **Methods:** The effects of a combined schedule of steroids and mycophenolate mofetil (MMF) was prospectively examined in a subset of IgAN patients with acute inflammatory histologic changes associated with proteinuria (mean 2,400 mg/day, range 1,130-5,250), hematuria (76 red cells per high-power microscopic field, range 30-100) and renal failure (serum creatinine 1.6 mg/dL, range 1.2-2.9). Patients had diffuse mesangial proliferation with at least 10% florid crescents, mild to moderate degrees of glomerular sclerosis and interstitial changes, and both mesangial and capillary deposition of immunoreactants at immunofluorescence. Treatment consisted of 3 pulses of methylprednisolone (15 mg/kg) followed by oral prednisone (0.8 mg/kg body weight, tapered until discontinuation within 4 months) and MMF 2 g for 6 months. **Results:** Serum creatinine, proteinuria and microscopic hematuria significantly dropped at 6 months compared with baseline values ($p=0.01$) and remained lower at the end of follow-up 51 months (range 24-90) later ($p<0.01$, for proteinuria and hematuria; $p=0.08$, for serum creatinine). **Conclusion:** Therapy with steroids and MMF may be considered in a subset of IgAN patients with florid glomerular changes, functional impairment and major urinary abnormalities, to prevent subsequent progression toward renal failure.

Key words: Glomerulonephritis therapy, IgA nephropathy, Mycophenolate mofetil.

Introduction

IgA nephropathy (IgAN) is a microcosm of glomerular lesions (1). Some histologic lesions are irreversible and progress toward obliteration of glomerular capillaries. Others are acute phlogistic processes potentially susceptible to reversal by means of immunosuppressive therapies. Therefore, it is difficult to identify truly

homogeneous subsets of patients for treatment trials, especially if the entry criteria are based on a single variable such as urinary protein excretion. This could possibly explain in part the conflicting results of reports on cytotoxic drugs in these patients (2). Based on the encouraging results of an open nonrandomized controlled study on IgAN patients with diffuse mesangial proliferation, florid crescents and a mild degree of glomerular sclerosis and tubulointerstitial changes, years ago we proposed administering a short course of therapy with prednisone and cyclophosphamide to this particular subset of patients (3). With the availability of the a priori less toxic mycophenolate mofetil (MMF), the effects of a combined schedule of steroids and MMF were prospectively examined in a subset of IgAN patients with inflammatory histologic changes associated with major urinary abnormalities and renal failure. The present prospective study reports on the longterm benefits of this scheme, in terms of preservation of renal function and changes in urinary abnormalities, in 8 patients who were followed up for 24-90 months (mean 51 months).

Patients and methods

Demographic and baseline clinical and histologic features of a sample of 8 patients with at least a 24-month followup are summarized in Tables I and II. Proteinuria and serum creatinine were measured by standard methods. Glomerular filtration rate was evaluated by the Modification of Diet in Renal Disease (eGFR-MDRD186) study equation, as recommended by the MDRD Study Group (4). Microscopic hematuria was determined at baseline and then every 6 months as a mean of the counts of 5 high-power microscopic fields (HPMF) in 3 consecutive evaluations in 7 to 13 days. On average, patients were treated within 1 month of the renal biopsy. Patients were considered eligible for the treatment if the following inclusion criteria were satisfied: presence of diffuse mesangial proliferation with at least 10% florid crescents, and mild to moderate degrees of glomerular sclerosis and interstitial changes with immunofluorescence pattern of capillary deposits of immunoreactants at the renal biopsy, in combination with major urinary abnormalities including proteinuria >1 g/24 hours, and microscopic hematuria >30 red blood cells/HPMF.

Exclusion criteria included presence of diabetes, severe osteoporosis, severe metabolic syndrome, concomitant infection, time from renal biopsy to study entrance more than 8 weeks and age less than 18 or more than 80 years. All patients could be classified as M1, S1, E1 and T1-2 according to the Oxford classification of IgA nephropathy (5). However, it should be noted that the Oxford classification does not shed any light on the predictive value of crescents or the immunofluorescence findings. Treatment consisted of 3 pulses of methylprednisolone (15 mg/kg each) followed by oral prednisone (0.8 mg/kg body weight, for 2 weeks, 0.6 mg/kg for another 2 weeks, 0.4 mg/kg for an additional 4 weeks, then slowly tapered by 5 mg every 2 weeks until discontinuation) and 2 g of MMF for 6 months. All patients were hypertensive, and 6 of them had already been treated for at least 3 months with the same dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptors blockers when starting with immunosuppressive drugs. Differences among study groups were analyzed by multifactorial ANOVA. Differences were considered statistically significant when 2-sided p values were <0.05. Statistical analyses were carried out using StatView 5.0.1 for Macintosh (SAS Institute, Cary, NC, USA). This study was performed according to the local rules for off-label therapy in the Piedmont Region (Northwest Italy).

Results

Serum creatinine (baseline levels 1.6 mg/dL, range 1.2-2.9), eGFR-MDRD186 (52.5 ml/min, range 16-86), proteinuria (2,420 mg/day, range 1,130-5,250) and even microscopic hematuria (mean baseline count of 3 separate examinations: 76 red blood cells [RBCs] per HPMF range 28-100) dropped significantly at 6 months (creatinine 1.08 mg/dL, range 0.7-2.1, $p=0.01$; eGFR-MDRD186 66.9 ml/min, range 24-118, $p<0.05$; proteinuria 845 mg/day, range 150-2,916, $p<0.01$ and microscopic hematuria 12.25 RBC/HPMF x 400, 0-25,

$p=0.01$) compared with pretreatment values. At 6 months, no differences were observed in blood pressure (systolic 120 ± 10 mm Hg, diastolic 82 ± 7 mm Hg) and serum albumin (4.1 ± 0.5 g/dL) compared with baseline values (systolic 125 ± 10 mm Hg, diastolic 80 ± 8 mm Hg; serum albumin 3.9 ± 0.5 g/dL). Significant differences were observed when baseline data were compared with those determined at the last observation 24-90 months (mean 51 months) later in proteinuria (652 mg/day, range 150-2,050) and microscopic hematuria (6.9 RBC/HPMF, range 0-25; $p<0.01$, in both cases), whereas differences in values of serum creatinine (1.1 mg/dL, range 0.7-2.0, $p=0.08$), eGFR-MDRD186 (71 ml/min, range 25-116, $p=0.09$), blood pressure (systolic 120 ± 10 mm Hg, diastolic 75 ± 8 mm Hg, $p=0.1$) and serum albumin (4.2 ± 0.6 g/dL, $p=0.9$) failed to reach statistically significant levels. Two out of 8 patients (SL and LGM in Tab. II) had serum creatinine values higher than their baseline levels (1.4 and 1.8 mg/dL vs. 1.2 and 1.4 mg/dL, respectively). General results are summarized in Table III and Figures 1, 2, 3 and 4. Drug side effects were negligible. Only 1 case, SC, reported transient diarrhea at the beginning of the therapy with MMF, which rapidly resolved with probiotic agents.

Discussion

Contradictory results have been reported on the use of MMF in IgAN. Initial open studies seemed to support its possible role in stabilizing renal function even in high-risk patients (reviewed in (2)). Subsequently, 4 randomized studies were published. As first-line therapy, MMF (1-1.5 g/day) was found to be superior to steroids in decreasing proteinuria and protecting renal function (6). In contrast, Maes et al (7), who compared MMF (2.0 g/day) with placebo, found no significant differences in proteinuria or renal function after a 3-year followup. In a third study, Frisch et al (8) found no benefit in "a priori" high-risk patients. By contrast, Tang et al reported some definite advantages in MMF as compared with conservative treatment (9). The main difficulty in interpreting the results of therapeutic trials in IgAN lies in the wide spectrum of the possible histologic lesions, which may be either acute phlogistic and potentially reversible, or sclerotic and putatively unresponsive to currently available antiinflammatory or cytotoxic drugs. Male prevalence, age at the time of biopsy (>30 years) and moderate to severe intracapillary and extracapillary lesions are generally considered prognostically important in IgAN. Crescentic glomerular involvement has occasionally been reported as resolving spontaneously, but has more recently been regarded as an indicator of unfavorable prognosis even if small and focal (1). Decreased renal function, hypertension and proteinuria over 1,000 mg/day were found to be independent risk factors for a poor clinical course of disease in several reports. All of these risk factors were often simultaneously present in our study group. Tang et al (10) extended their original study by following 40 Chinese patients with established IgAN for 6 years. All patients were maintained on their angiotensin blockade (30 under ACE-inhibitor and 10 under angiotensin receptor blockade) medication, and half were randomized to receive MMF for 6 months. After 6 years, 11 patients required dialysis (2 from the MMF and 9 from the control group). The authors concluded that among Chinese patients with IgAN who had mild histologic lesions and persistent proteinuria despite maximal angiotensin blockade, MMF treatment may result in transient and partial remission of proteinuria in the short term and renoprotection in the long term. Our patients fell into histologic categories usually thought to be at risk of progression, and our data substantially confirm the results of Tang et al. It was emphasized that the conflicting effects obtained by MMF administration might reflect differences in the disease process, differences in MMF metabolism or varying responses to the immunosuppressive agent in different populations (2). We speculate that the presence of florid inflammatory processes, as documented by mesangial hyperplasia, intracapillary and extracapillary proliferation, and accumulation of leukocytes in the capillary lumina may be prerequisites for a response to the immunosuppressive therapy in IgAN, proteinuria being a uniform expression of both florid inflammatory and sclerotic changes. Cyclophosphamide proved to be effective in preserving renal function

in the long run in these cases (3). However, infertility and malignancies (especially in the long-term treatment) in the young patient, and leukopenia and infections in the elderly, make this treatment unappealing and the advent of effective and safer forms of management more than welcome. A recent randomized controlled trial in patients with normal or slightly reduced renal function failed to demonstrate a greater efficacy of low-dose azathioprine added to steroids compared with steroids alone (11). However, the effects of azathioprine in high-risk patients, similar to the cohort of the present study, is still under the evaluation of the same multicenter research group. The short courses of therapy with steroids and MMF that were prospectively administered in this open trial seemed to be as effective as cyclophosphamide in a subset of IgAN patients with florid inflammatory changes, renal impairment and major urinary abnormalities, possibly preventing subsequent progression toward renal failure. We believe there is still a rationale for promoting new controlled studies with large sample sizes and long follow-up duration on high-risk patients homogeneously selected based on kidney histology, functional impairment and severe urinary abnormalities.

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TABLE I BASELINE CHARACTERISTICS OF THE STUDY POPULATION

Number of patients	8
Sex, M/F	6/2
Mean age, years	47 (range 21-76)
Time from biopsy to study entry, weeks	1.2 (range 1-7)
Serum creatinine, mg/dL	1.6 (range 1.2-2.9)
Mean urinary protein excretion, mg/day	2,417 (range 1,130-5,250)
Number of patients with nephrotic syndrome	3
ACEi/ARB therapy, number of patients	6
RBC/HPMF $\times 400$	76 (range 30-100)
Number of hypertensive patients	8

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blockers; RBC/HPMF = red blood cells per high-power microscopic field.

TABLE II HISTOLOGIC FEATURES OF THE STUDY POPULATION

Patient	G	M	GS	TI	C	CEI
SL	13	+	6 G	+	(2/13)	+
SA	8	+	1 F	+ (moderate)	(1/8)	+
BR	37	+	17 G, 4 F	+	(4/37)	+
CT	10	+	1 F	+ (moderate)	(2/10)	+
LGM	8	+	1 G, 5 F	+	(1/8)	+
MM	9	+	1 G	+ (moderate)	(1/9)	+
SM	8	+	1 G, 2 F	+	(1/8)	+
SC	14	+	3 G	+	(2/14)	+

C = crescents (affected glomeruli); CEI = capillary extension of immune reactants; G = number of glomeruli; GS = glomerular sclerosis (G: global, F: focal); M = diffuse mesangial hyperplasia; TI = tubulointerstitial infiltration.

TABLE III PATIENT CATEGORIES ACCORDING TO URINARY PROTEIN EXCRETION BEFORE AND AFTER TREATMENT

	<0.3 g/day	0.3-2.0 g/day	>2.0 to 3.5 g/day	> 3.5 g/day
Baseline	0	5	0	3
6 months later	4	3	1	0

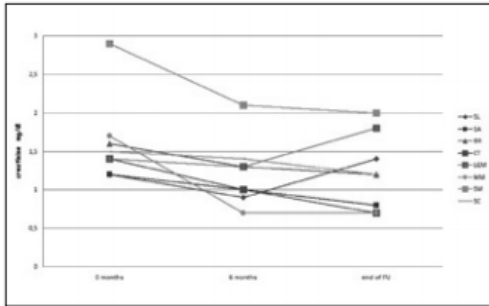


Fig. 1 - Serum creatinine (mg/dL) during the follow-up period. Follow-up (FU) duration: SL 85 months, SA 66, BR 43, CT 46, LGM 90, MM 24, SM 24 and SC 30. Compared with baseline values, the decrease was significant at 6 months ($p=0.01$).

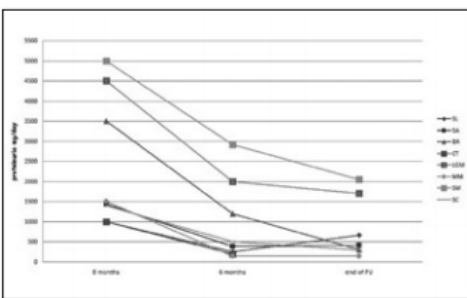


Fig. 2 - Proteinuria (mg/day) during the follow-up (FU) period. Follow-up duration: SL 85 months, SA 66, BR 43, CT 46, LGM 90, MM 24, SM 24 and SC 30. Compared with baseline values, the decrease was significant at 6 months and at the end of follow-up ($p<0.01$, in both cases).

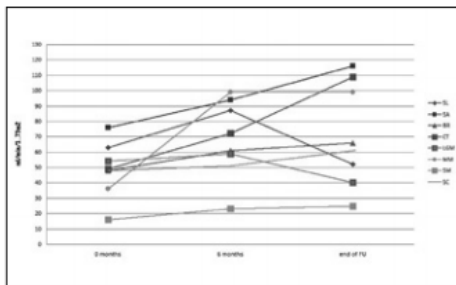


Fig. 3 - Profile of glomerular filtration rate (eGFR-MDRD186, ml/min per 1.73 m²) during the follow-up (FU) period. Followup duration: SL 85 months, SA 66, BR 43, CT 46, LGM 90, MM 24, SM 24 and SC 30. Compared with baseline values, the increase was significant at 6 months ($p<0.05$).

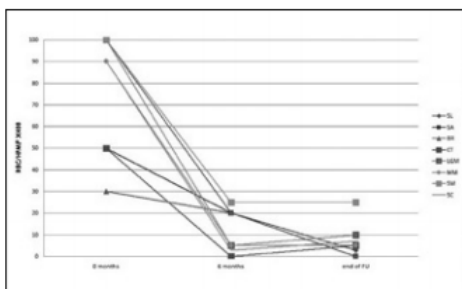


Fig. 4 - Red blood cells/high-power microscopic field (RBC/ HPMF) $\times 400$ (number/ μ L) during the follow-up period. Followup (FU) duration: SL 85 months, SA 66, BR 43, CT 46, LGM 90, MM 24, SM 24 and SC 30. Compared with baseline values, the decrease was significant both at 6 months ($p=0.01$) and at the end of follow-up ($p<0.01$).