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Treatment of mesangiocapillary glomerulonephritis with alternate-day prednisone – a report of The International Study of Kidney Disease in Children

Penina Tarshish[1], Jay Bernstein[2], Jonathan N. Tobin[1], and Chester M. Edelmann Jr [1]

[1] Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, New York, USA
[2] William Beaumont Hospital, Royal Oak, Michigan, USA

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Abstract. It has been claimed that long-term prednisone treatment ameliorates the course of children with mesangiocapillary glomerulonephritis (MCGN). The International Study of Kidney Disease in Children conducted a randomized, double-blinded, placebo-controlled clinical trial in 80 children with idiopathic MCGN, including 42 patients with type I disease, 14 with type II disease, 17 with type III disease, and 7 with nontypable disease. Criteria for admission included heavy proteinuria and a glomerular filtration rate of greater than or equal to 70 ml/min per 1.73 m^2. Prednisone or lactose, 40 mg/m^2, was given every other day as a single morning dose. The mean duration of treatment was 41 months, renal failure being the most common reason for termination of therapy. Treatment failure was defined as an increase from baseline of 30% or more in serum creatinine, or more than 35 μmol/l. Overall, treatment failure occurred in 55% of patients treated with lactose, compared with 40% in the prednisone group. Life-table analysis showed a renal survival rate (i.e., stable renal function) at 130 months of 61% among patients receiving prednisone and 12% among patients receiving lactose ($P = 0.07$). Of patients with type I or III MCGN, 33% treated with prednisone were treatment failures, compared with 58% in the lactose group. Long-term treatment with prednisone appears to improve the outcome of children with MCGN.

Key words: Mesangiocapillary glomerulonephritis – Prednisone – Controlled trial

Introduction

Mesangiocapillary glomerulonephritis (MCGN) is a chronic disease with relentless progression to end-stage renal failure. The frequency of MCGN varies with the population studied: 8% of patients presenting with symptoms of persistent or chronic nephritis [1], 11% of patients with heavy proteinuria [2], and 7.5% of children presenting with nephrotic syndrome [3]. It is primarily a disease of children, adolescents, and young adults, with a predominant age distribution at presentation of 6–30 years [4–7]. It is uncommon before 6 years of age [1, 3]. The female: male sex distribution is approximately 60:40, most studies showing a small female preponderance [1, 3, 5, 6, 8, 9].

Studies of the natural history of this disease have shown progression to end-stage renal disease in 50% of patients at 6 years [5], 10 years [4], or 11 years [1], while the yearly mortality rate during the first 10 years was found to be 6.4% [1]. Twenty years after the onset of the disease, 90% of patients are in renal failure and 10% are in remission, with or without normal renal function [4, 8].

Drug regimens for the treatment of MCGN have included cytotoxic, immunosuppressive, antiplatelet, and antithrombotic agents [4, 5, 9–19], singly or in various combinations. Most of these attempts have been uncontrolled and retrospective and have yielded equivocal results [20]. This was especially true in the early 1970s, when there was no evidence that any drug altered the course of this disease. Therefore, the International Study of Kidney Disease in Children (ISKDC) undertook a controlled, double-blinded trial, in which patients were randomized to long-term, low-dosage therapy with either prednisone or lactose.

Methods

Selection of patients. Between February 1970 and October 1980, 91 children were available for entry into the MCGN trial. Of these, 80 children, ranging in age from 5.2 to 16.9 years, were admitted. Informed consent was obtained in each case. Eleven children were excluded owing to lack of parental consent, histopathological confirmation, or further follow-up.

Criteria for admission to the trial were as follows: (1) biopsy-proven MCGN as defined below, (2) glomerular filtration rate measured by creatinine clearance of greater than or equal to 70 ml/min per 1.73 m^2, (3) heavy proteinuria greater than or equal to 40 mg/h per m^2 determined quantitatively on an overnight collection, (4) no evidence of systemic lupus erythematosus, Henoch-Schoenlein purpura, nephritis accompanying bacteremia (such as bacterial endocarditis), or malaria, and (5) no

Offprint requests to: C. M. Edelmann Jr

treatment with corticosteroids during the year prior to entry into the trial or with immunosuppressive agents at any time.

Trial procedure

Following admission to the study, patients were allocated by the central office of the ISKDC according to a random design, balanced within every series of 4 patients both within and between participating clinics, to a double-blinded regimen of prednisone or placebo (lactose). Of the 80 patients entered into the study, 47 were randomized to prednisone and 33 to placebo. This unequal distribution of patients is within reasonable bounds of chance and reflects the fact that not all clinics admitted multiples of 4 patients. All assessments of outcome were done prior to unblinding the study. Medication for each patient was supplied by the central office. The treatment regimen consisted of either prednisone or placebo, 40 mg/m^2, every other day for 5 years, given in a single dose in the morning, with a maximum dosage of 60 mg. Patients were monitored for prednisone-related toxicity and undesirable side effects throughout the trial, including glycosuria, hypertension, steroid-related obesity, hirsutism, seizures, increased incidence of infection, and growth retardation.

Histopathological description

Renal biopsies were to be performed at entry, and after 2 years and 5 years. Although the majority of biopsies were performed at the stipulated times, others were done over a follow-up period of 1–7 years. Renal biopsy specimens were interpreted without knowledge of clinical data by a central group of four pathologists (J. Churg, R. Habib, R. H. R. White, J. Bernstein). Criteria and definitions of MCGN were those previously established by the ISKDC [21], as modified by the more recent World Health Organization *Classification and Atlas of Glomerular Diseases* [22].

Type I MCGN (subendothelial deposits). The glomerular capillary walls are thickened and accompanied by variable degrees of mesangial cell proliferation and by variable increases in mesangial matrix. The capillary wall thickening results from subendothelial deposits and mesangial interposition, with the formation of a new subendothelial lamina of glomerular basement membrane (GBM) and the appearance of a duplicated or split GBM (double-contour). The deposits, while partly subendothelial, are more prominently present in the mesangium and in the areas of mesangial interposition. MCGN is usually diffuse, occasionally focal in distribution. The increased mesangial cellularity and matrix may lead to an accentuation of the lobular structure of the glomerulus, so-called lobular glomerulonephritis.

Type II MCGN (dense-deposit disease). Glomerular capillary walls are diffusely thickened in association with variable mesangial hypercellularity and variably increased mesangial matrix. Lobular accentuation occurs, as in type I MCGN, but is less prominent. The capillary wall thickening is caused by dense deposits within the lamina densa of the GBM. Mesangial interposition and double-contour are variably present. Focal type II MCGN, involving a proportion of glomeruli, occurs occasionally.

Type III MCGN (transmembranous deposits). The glomerular abnormality of type III MCGN is similar to that of type I, except that the GBM appears to be interrupted by transmembranous deposits. There is, therefore, a loss of normal GBM argyrophilia, as seen in periodic acid-silver methenamine stains, and subepithelial deposits are often prominent.

Histopathological assessment. Sections, usually unstained, were received from participating clinics and stained with hematoxylin and eosin, Masson's trichrome, periodic acid-Schiff, and periodic acid-silver methenamine stains. Sections in each case were evaluated by the central group of pathologists without knowledge of patient's age, sex, outcome, treatment protocol, or any clinical data, except that repeat biopsies from the same patient were identified for comparison with earlier biopsies. Sections were examined for total number of glomeruli and numbers of glomeruli with global sclerosis, segmental sclerosis, crescents, and adhesions. Other abnormalities were evaluated on an arbitrary scale of absent/normal (0), mild (1+), moderate (2+), and severe (3+): capillary wall abnormalities, mesangial hypercellularity, mesangial matrix, neutrophil infiltration, tubular atrophy and interstitial fibrosis, and hyaline vasculopathy. Light microscopic impressions were confirmed by electron-microscopic examinations carried out in one laboratory (J. Bernstein) and reviewed at meetings of the central group of pathologists.

Methods used for data collection, coding, and reporting, and for clinical and laboratory examinations have been described [3]. All laboratory determinations were performed blinded to treatment allocation.

Definitions

Treatment failure (used as the trial end-point): increase from baseline in serum creatinine of either 30% or more, or more than 35 µmol/l (0.4 mg/dl).

Stable renal function: no change or increase in serum creatinine of less than 30% and less than 35 µmol/l.

Renal failure: increase in serum creatinine to greater than or equal to 350 µmol/l (>4.0 mg/dl).

Hematuria: more than 30,000 RBC/h per m^2 in an overnight collection of urine or more than 2 RBC/m^3 in an untimed, uncentrifuged urine specimen, or positive dipstick test.

Proteinuria: greater than or equal to 4 mg/h per m^2 in an overnight urine collection.

Resolution of hematuria or proteinuria: normalization in three consecutive specimens or two specimens over at least an 18-month period.

Statistical methods

All statistical analyses were performed using version 5 of the Statistical Analysis System (SAS, Institute, Cary, N.C.) on an IBM 3270 mainframe and versions 6.03 and 6.04 on an AT-compatible 386 personal computer [23]. For comparisons between proportions, one-tailed and two-tailed Fisher's exact tests[1] and chi-square analyses were performed. For continuous measures, *t*-tests were performed to test for differences between lactose and prednisone groups. A Cox proportional hazards regression model [23, 24] was used to examine the baseline histological variables in relation to treatment outcome, while controlling for disease type (I, III versus II) and treatment allocation for 61 subjects with complete histological data (histological data were not available for 9 prednisone and 6 lactose patients, type was not available for 5 prednisone and 6 lactose patients, type was not available for 5 prednisone and 2 lactose patients). The Cox proportional hazards regression model is a survival analysis that allows the censoring of follow-up times for patients who are lost to follow-up or who withdraw from the study early.

[1] The question posed in this trial was whether adrenocortical steroid therapy as compared with placebo would improve the outcome of MCGN. It did not include the question whether placebo would improve the outcome as compared with steroid, since no difference between the two groups or a worse outcome in the prednisone group would lead to the same conclusion: prednisone should not be used. Therefore, Fisher's exact test was applied as a one-tailed analysis. For completeness, two-tailed analyses are also presented. All other statistical calculations were based on a two-tailed analysis

Table 1. Baseline clinical characteristics in patients with mesangiocapillary glomerulonephritis (MCGN) randomized to prednisone or lactose therapy (mean ± SEM)

	Prednisone ($n = 47$)	Lactose ($n = 33$)
Age at diagnosis (years)	10.1 ± 0.37	9.4 ± 0.54
Age at entrance (years)	10.8 ± 0.36	11.1 ± 0.50
Sex (M/F)	24/23	19/14
Duration of disease prior to entry (months)	8.9 ± 1.3	18.1 ± 3.9*
GFR[a] at entrance (ml/min per 1.73 m^2)	112 ± 5.8	108 ± 6.2
BP systolic (mmHg)	122 ± 2.3	123 ± 3.2
diastolic (mmHg)	75 ± 2.3	75 ± 2.3
Plasma creatinine (µmol/l)	62 ± 22	70 ± 52
Serum albumin (g/l)	24 ± 1.2	27 ± 1.7
Serum C_3 (g/l)	0.14 ± 0.04	0.12 ± 0.05
Urine RBC/h per m^2 (× 1,000)	1,140 ±375	1,313 ±557
Urine protein (mg/h per m^2)	122 ± 13.7	113 ± 14.6
Type I	24	18
Type II	9	5
Type III	9	8
Untyped	5	2

* $P < 0.05$

GFR, Glomerular filtration rate; BP, blood pressure; RBC, red blood cells

[a] Creatinine clearance

Since the distribution of follow-up times was variable within each treatment group (although the mean length of follow-up did not differ between the two groups), the distribution of time to failure has been estimated by the Kaplan-Meier product limit method. The horizontal axis is the months of follow-up and the vertical axis is the percentage of patients still stable (i.e., without treatment failure). The distribution function of failure time is a step function. When there is failure, the percentage of patients who are still stable will drop at the time of failure. When there is a drop-out, the percentage stable remains the same. The survival curve for patients on prednisone is different from that for the placebo group overall with $P < 0.07$ [25, 26]. All subjects were included in the analyses and were analyzed in the treatment group to which they were initially randomized, regardless of noncompliance or premature withdrawal from treatment.

Results

Onset characteristics

Baseline characteristics of the experimental and control groups at the time of entry into the trial were comparable with regard to age at onset of disease and at entrance into the study, sex, blood pressure, glomerular filtration rate, serum creatinine concentration, and histopathological type of disease (Table 1). Histopathological typing was not available in 7 patients in whom the pathologists were unable to subclassify the glomerular abnormality. The experimental and control groups were also comparable for initial values of serum urea, cholesterol, total protein, albumin, and C_3, as well as hematuria, pyuria, and rates of excretion of urinary protein.

The mean duration of disease prior to initiation of treatment was significantly greater in the control than in the experimental group, a difference that could not be explained. Follow-up time from entry into the trial was equivalent, with a mean of 63 months in each group, and extending up to 170 months.

Since it is the opinion of some nephrologists and renal pathologists that types I and III MCGN are the same disease entity, but are different from type II [4, 27, 28], we analyzed the data for type I and type III together and for type II separately. A comparison of baseline characteristics among types I and III patients randomized to either prednisone or lactose treatment showed that, in parallel with the above findings for all three types, the two treatment groups were equivalent. However, as noted in the analysis combining all types, lactose-treated patients had a statistically significant longer time between onset of disease and initiation of therapy than did prednisone-treated patients ($P = 0.03$). Baseline characteristics as described above were also similar for the two treatment groups for type II patients.

Duration of therapy

The duration of drug therapy was equivalent for each group, with a mean treatment period of 41 months. The most common reason for cessation of therapy prior to 60 months was renal failure, which occurred in 22 patients (9 prednisone, 13 lactose). (Five additional patients who developed renal failure completed the full course of therapy). Other causes of premature withdrawal from treatment included treatment error and noncompliance (6 patients, 5 prednisone, 1 lactose), patient refusal (1 patient, prednisone), growth failure (1 patient, prednisone), and loss to follow-up (1 patient, lactose). Treatment of 7 patients was discontinued because of development of hypertension (5 prednisone, 2 lactose); hypertensive encephalopathy occurred in 5. Of the 5 patients with hypertensive encephalopathy, 2 were receiving placebo, attesting to the importance of hypertension in the natural history of this disease. In the 2 hypertensive patients who did not develop encephalopathy, treatment was stopped because of "steroid toxicity", i.e., hypertension, osteoporosis, mild diabetes mellitus, and obesity.

Prednisone-treated patients had an increased incidence of steroid-related obesity, but they were similar to the lactose-treated patients with regard to degree of hirsutism and frequency of infection and glycosuria.

Outcome

All patients entered into the trial were included in the outcome analysis. Among patients treated with lactose, 55% were considered treatment failures by the end of the follow-up period, compared with 36%–40% treatment failures in the prednisone group (Table 2). Since the follow-up time was variable, with the upper limit 170 months, Kaplan-Meier analysis was performed, and showed at 130 months 61% of patients receiving prednisone were stable, without treatment failure or renal failure, compared with 12% of patients receiving lactose ($P = 0.07$) (Fig. 1).

Of the 34 patients who fulfilled the definition of treatment failure, 27 developed renal failure (serum creatinine

Table 2. Treatment failure

	Prednisone		Lactose		Fisher's exact	
					one-tailed	two-tailed
All patients ($n = 80$) Status known	16/44	36.4%	18/33	54.5%	0.087	0.164
Including 3 status unknown	19/47	40.4%	–	–	0.154	0.258
Types I, III ($n = 59$) Status known	9/31	29.0%	15/26	57.7%	0.028	0.035
Including 3 status unknown	11/33	33.3%	–	–	0.054	0.071
Type II ($n = 14$) Status known	5/ 9	55.6%	3/ 5	60.0%	0.657	1.0
Type unknown ($n = 7$) Status known	2/ 4	50.0%	0/ 2	0%	0.400	0.467
Including 1 status unknown	3/ 5	60.0%	–	–	0.286	0.429

>350 μmol/l) sometime during the course of observation, validating the definition of treatment failure that was used as the end-point of the trial. Of these, 13 were assigned to prednisone and 14 to lactose. Six died: 2 in the prednisone group and 4 in the lactose group.

The outcome in types I and III disease paralleled the study as a whole and provided even stronger evidence for the efficacy of prednisone in this disease. Of patients receiving prednisone, 29%–33% were treatment failures at last follow-up versus 58% of patients receiving lactose (Table 2).

Of patients with type II disease, 44% of the prednisone group and 40% of the lactose group were stable at last follow-up. However, with the total number of type II patients limited to 14, it is not possible to assess the efficacy of prednisone in this subgroup.

Characteristics related to treatment failure

In each treatment group, the percentage of patients remaining stable (i.e., not classified as treatment failure) is shown for those above the median value of each characteristic or at or below the median value (Table 3). Blood pressure at onset did not predict the subsequent course in either the prednisone or lactose group, i.e., the percentage of patients remaining stable was not different when comparing those with the higher or lower values of systolic or diastolic pressure. In the lactose group, patients with a less severe nephrotic syndrome at onset, as evidenced by significantly higher values of glomerular filtration rate, serum total protein, and serum albumin, and with significantly lower values of serum cholesterol and urinary protein, were more likely to remain stable, i.e., not to qualify as treatment failure ($P < 0.05$). In contrast, these variables in the prednisone group were not predictive of the subsequent course.

Serum albumin levels at the end of the trial were not significantly different in the lactose-treated and prednisone-treated groups ($P = 0.9$). However, when the groups were subdivided into failed and stable patients, there was a significant difference across the four subgroups ($P = 0.0015$), with failed patients having lower serum albumin levels. This is a reflection of the correlation between outcome and final albumin levels ($r = 0.42$, $P = 0.0003$).

Table 3. Percentage of patients in each treatment group remaining stable, related to baseline characteristics (risk factors)[a]

Baseline characteristic		Prednisone ($n = 46$)	Lactose ($n = 33$)
BP (mmHg)			
Systolic	>120	55.0	35.7
	≤120	64.0	52.6
Diastolic (change)	> 80	44.4	55.6
	≤ 80	69.6	42.1
Diastolic (disappearance)	> 75.5	50.0	41.7
	≤ 75.5	62.5	63.6
GFR[b] (ml/min per 1.73 m^2)			
	≤106.8	55.0	25.0*
	>106.8	76.5	61.1
Serum protein (g/l)			
	≤ 4.85	64.0	7.1*
	> 4.85	52.6	73.7
Serum albumin (g/l)			
	≤ 2.4	65.4	26.7*
	> 2.4	61.5	64.3
Serum cholesterol (mmol/l)			
	> 7.62	65.2	16.7*
	≤ 7.62	55.6	57.9
Urine protein (mg/h per m^2)			
	> 96	72.7	35.3*
	≤ 96	50.0	56.3

* $P \leq 0.05$ within the lactose group

[a] For each characteristic, patients were divided into two groups, those above the median and those at or below the median

[b] Creatinine clearance

The long-term effect of steroid therapy is difficult to assess. Stable patients were followed after discontinuation of prednisone therapy for a mean of 37.7 months with a range of 3–121 months. Seven patients failed after withdrawal from prednisone therapy; the mean time interval from withdrawal to treatment failure was 20.4 months, with a range of 4–47 months.

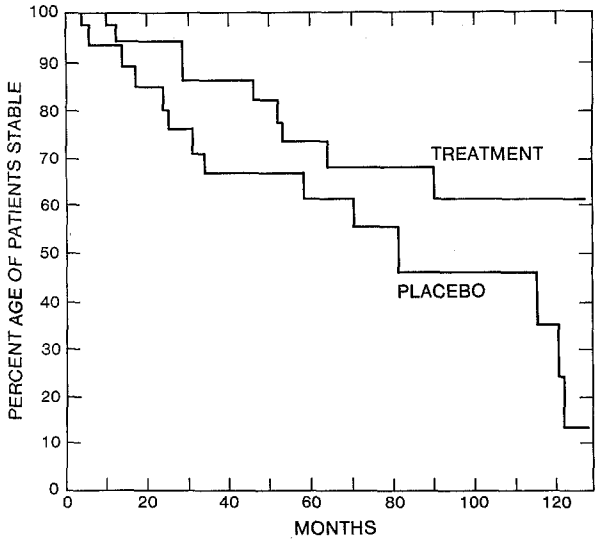

Fig. 1. Life-table analysis of patients with types I, II, and III mesangiocapillary glomerulonephritis. Kaplan-Meier estimates of percentage of patients remaining stable over time. The analysis at 60 months included 22 patients in the treatment group and 17 patients in the placebo group; at 90 months, 11 treatment and 7 placebo; and at 120 months 4 treatment and 6 placebo

Hematuria and proteinuria

Resolution of both hematuria and proteinuria occurred in only 6 patients, equally divided between the two treatment groups. Their renal function remained stable for the duration of the study, with a mean follow-up time of 63 months. Hematuria resolved in 14 of 65 patients (21%), of whom 8 lost their hematuria without resolution of proteinuria. Five were receiving prednisone and 3 lactose. Three of the patients whose hematuria alone resolved went on to renal failure – 2 treated with lactose, 1 with prednisone. The majority of our patients had persistent proteinuria. A small number (5) had intermittent proteinuria, and only 2 patients had resolution of proteinuria alone.

Renal histopathology

The majority of the patients had diffuse proliferative lesions, only 4 having focal and segmental disease. Of the 4, 2 were found to be randomized to prednisone and 2 to lactose therapy. Renal glomerular histopathology at baseline was equivalent for the prednisone and lactose patients and for failed and stable patients within each treatment group when evaluated semiquantitatively for global and segmental sclerosis, crescents, and adhesions and synechiae. Additional histopathological features, including abnormal capillary walls, mesangial cellularity, mesangial matrix expansion, polymorphonuclear infiltration, tubular atrophy with interstitial fibrosis, and vascular hyalinization, also were equivalent for the two groups.

In order to examine the effects of baseline histological variables controlling for drug allocation and type (I, III versus II), a Cox proportional hazards regression analysis was performed (Table 4). The histological abnormalities

Table 4. Cox proportional hazards regression analysis of initial biopsy, type, and treatment, as predictors of treatment failure

Variable	Coefficient ± SE	*P* value	Risk ratio
Total glomeruli[a]	–0.02±0.02	0.15	1.0
Global sclerosis	–0.16±0.09	0.08	0.85
Crescents	0.16±0.13	0.22	1.18
Segmental sclerosis	0.19±0.13	0.15	1.21
Abnormal capillary walls	0.62±0.45	0.16	1.87
Mesangial cells	–0.92±0.48	0.05	0.40
Mesangial matrix	–0.23±0.42	0.59	0.80
Polymorphonuclear leukocytes	0.21±0.22	0.36	1.23
Tubular atrophy, interstitial fibrosis	0.45±0.30	0.13	1.57
Treatment	0.17±0.48	0.72	1.19
Type	–0.98±0.76	0.19	0.37

[a] This variable was entered into the proportional hazards regression model [24] as a covariate to adjust for differences in biopsy size, and was retained in the model to adjust all of the variables for differences in total glomeruli across individuals

Table 5. Changes in histology in patients with type I or type III MCGN from initial to last biopsy by treatment allocation[a]

		Prednisone	Lactose	Fisher's exact (one-tailed)
Global sclerosis	IMP/NC	9	5	0.29
	Worse	14	14	
Crescents	IMP/NC	23	18	0.45
	Worse	0	1	
Segmental sclerosis	IMP/NC	15	8	0.11
	Worse	8	11	
Abnormal capillary walls	IMP/NC	22	18	0.70
	Worse	1	1	
Mesangial hypercellularity	IMP/NC	23	19	1.0
	Worse	0	0	
Increased mesangial matrix	IMP/NC	20	17	0.59
	Worse	3	2	
Polymorphonuclear leucocytes	IMP/NC	22	18	0.69
	Worse	1	1	
Tubular atrophy and interstitial fibrosis	IMP/NC	12	10	0.61
	Worse	11	9	

IMP, Improved or decreased; NC, no change

[a] Twenty-six patients (15 prednisone, 11 lactose) had a single follow-up biopsy, 16 patients (8 prednisone, 8 lactose) had two or more follow-up biopsies

that were statistically significant predictors of treatment failure were: lower levels of global sclerosis ($P = 0.08$) and lower levels of mesangial hypercellularity ($P = 0.05$). Other predictors that did not achieve but approached statistical significance in this model included: segmental sclerosis (higher levels fail more often, $P = 0.15$), abnormal capillary walls (higher levels fail more often, $P = 0.16$), tubular atrophy with interstitial fibrosis (higher levels fail more often, $P = 0.13$) and type (type II fail more often than types I and III, $P = 0.19$).

Eighty-five follow-up biopsies were available from 55 patients. A combined analysis of type I and III patients showed that the proportion of patients whose biopsies improved or remained unchanged was equivalent in the prednisone and lactose groups (Table 5). In both the experimental and control groups, global sclerosis increased during the trial. More than half the patients in the lactose group had worsening segmental sclerosis, compared with one-third of the prednisone group. Tubular atrophy and interstitial fibrosis worsened in about half the patients in each group. The other histological features improved or remained unchanged.

Discussion

Multiple drug regimens have been utilized in the treatment of patients with MCGN, with variable results [20, 29]. Anticoagulants have been used in various combinations with immunosuppressive agents. Kincaid-Smith [13], in a retrospective uncontrolled trial, reported that a combination of cyclophosphamide, dipyridamole, warfarin, and heparin improved survival at 30 months in adult patients when compared with historical data. Similar results were observed in an uncontrolled study of ten children [14]. Survival was not improved with uncontrolled use of similar regimens in three other studies [4, 5, 9]. Anticoagulant therapy was of no benefit in a controlled trial in Australia [15] in which patients were treated with cyclosphosphamide, dipyridamole, and warfarin. Moreover, the study was plagued by a high drop-out rate owing to drug toxicity. A controlled trial in Canada [19] also failed to reveal a beneficial effect of 18 months of treatment with cyclophosphamide, Coumadin (warfarin, Du Pont Pharm, Wilmington, Delaware), and dipyridamole.

Promising results have been shown with warfarin and dipyridamole [17], and aspirin and dipyridamole [11]. However, the first study could not be analyzed conclusively owing to its cross-over design and the large number of hemorrhagic complications that occurred. In the second study, by Donadio et al. [11], the initial observations suggested that fewer patients in the treatment group progressed to advanced renal failure than in the placebo group. However, the 10-year cumulative survival free of renal failure was 49% in the platelet-inhibited group and 41% in the placebo group, a difference that is not statistically significant [20].

The trial reported here is the only randomized, controlled prospective study using prednisone alone. West [10] and McEnery et al. [12, 16, 30] have published uncontrolled, retrospective studies in children, utilizing an initial alternate-day dose of prednisone of 60 mg/m^2, maximum dose of 80 mg, with a subsequent slow reduction in dosage, and yielding impressive results. They showed actuarial renal survival, in 71 patients, of 82% in the 10th year and 56% in the 20th year after diagnosis. It is difficult to compare our results with these since the studies were not only different in design and dosage of prednisone but also in definition of treatment failure. Whereas McEnery et al. used a serum creatinine concentration of greater than 265 μmol/l (3.0 mg/dl) to define treatment failure, we used the more stringent criterion of a 30% increase or a rise of more than 35 μmol/l (0.4 mg/dl) of serum creatinine from baseline. Therefore, our renal survival in prednisone-treated patients of 61% at 10 years is comparable to their renal survival of 75%.

McEnery et al. [16] reported a striking difference between the response of 25 patients starting the regimen within 1 year of diagnosis and those of 20 patients in whom the regimen was started later. However, no such difference was found in the present study among patients in the prednisone group.

The greater duration of disease prior to entry in the placebo group could suggest a greater degree of progression, negatively impacting the outcome in this group. This was not considered to be a factor, however, since no other baseline variable differed between the two groups, most importantly magnitude of proteinuria, levels of serum creatinine and albumin, value of creatinine clearance, and histological features on renal biopsy. Furthermore, in neither the steroid nor the placebo group did outcome correlate with duration of disease prior to entry. In the present study, prednisone appeared to improve the prognosis of patients with types I and III MCGN by slowing the progression to end-stage renal failure. Patients treated with prednisone over an average of 41 months and followed for up to 14 years, with a mean of 5 years, had a 29%–33% treatment failure rate compared with 58% in the control group (Table 2).

In comparison to the difference in rates of treatment failure between prednisone-treated and lactose-treated patients in types I and III disease, the difference observed in the total group was diluted by the absence of a difference in outcome among the type II patients. In addition, the inability to achieve an overall level of significance of less than 0.05 may have been due to the small sample size. It should be noted that for the total group, the power to detect a difference of the size we found (36%–40% versus 55%) at alpha = 0.05, one-tail, was only 0.35. For a one-tail alpha = 0.05, in order to achieve a power of 0.80, we would have needed 95 subjects in each group, more than double the actual experience.

It is well established that renal insufficiency and the presence of nephrotic syndrome at onset in patients with MCGN are poor prognostic signs [1, 4]. All patients in the current study had nephrotic syndrome. However, its importance as a predictor of renal failure was noted only in the lactose-treated group. A significantly smaller percentage of lactose-treated patients with lower glomerular filtration rates and a more severe nephrotic syndrome at entry remained stable (Table 3). In contrast, these characteristics at entry were *not* predictors of failure in prednisone-treated

patients, suggesting that prednisone ameliorated the course of the disease to the extent that it eliminated these variables as risk factors.

As would be expected, the extent of segmental sclerosis, capillary wall abnormalities, and tubular atrophy with interstitial fibrosis was predictive of treatment failure. The inverse correlation between the degree of mesangial hypercellularity and the frequency of treatment failure could not be explained.

It is difficult to account for the lack of correlation between the clinical and histological outcomes in the prednisone and lactose groups. This is contrary to some reports [16, 18], but is supported by Strife et al. [31], who noted that the correlation between clinical and pathological outcome in type III MCGN was not consistent. Other randomized treatment trials cannot be analyzed for such correlations, because they did not include follow-up renal biopsies [11, 17, 19]. The increasing global sclerosis in both the prednisone and lactose groups is in agreement with other data [16], and probably indicates progression of immunological injury that began prior to institution of the regimen.

Our data do not permit the assessment of the long-term effects of prednisone therapy. It should be noted, however, that patients who failed after withdrawal from treatment with prednisone did so within a relatively short period of time.

One must consider the possibility that a higher initial prednisone dosage, such as that used by McEnery et al. [12], would have improved the outcome. However, even with the relatively low prednisone dose of 40 mg/m^2 on alternate days used in this trial, hypertensive encephalopathy and other adverse side effects of steroid therapy were encountered. Although this is in contrast to the minimal toxicity encountered by McEnery et al. [12], steroid toxicity in their series may have been ameliorated by reduction in dosage over time.

It appears from our study that normalization of both urinary red cell and protein excretion is a favorable prognostic sign, since all patients who did so remained stable. This may be helpful in determining when prednisone should be decreased or withdrawn. However, disappearance of both hematuria and proteinuria occurred in only 6 patients out of the entire group. McEnery et al. [16] found disappearance of hematuria alone to be a favorable prognostic sign. Since this occurred in only 8 patients in our series, 3 of whom went on to renal failure, we cannot confirm their finding. Our data do not provide information on the prognostic value of the disappearance of proteinuria alone, since this occurred in only 2 patients.

In conclusion, this study suggests strongly that alternate-day prednisone therapy improves the prognosis of patients with MCGN, when used at doses of 40 mg/m^2. Careful monitoring for adverse side effects of treatment and aggressive therapy of hypertension are necessary.

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Announcement

XXIVth International Conference on Transplantation and Clinical Immunology, Lyon, France, June 1, 2 and 3, 1992.

Evaluation and Monitoring in Transplantation "Toward an optimal control"

Topics:

- Histocompatibility: Which techniques?
  For which compatibility?
- Pretransplant transfusion: Yes or No.
- Immunosuppression: evaluation and adaptation
- Which treatment for high risk patients?
- Evaluation of early and late surgical complications.
- Quality of the graft.
- Xenografting and solutions for organ shortage.
- Rejection monitoring; Cytokines involvement.

Participants to the Course are invited to present posters on Transplantation and in particular on the above mentioned subjects.

Information:
Isabelle Guillaumond
CITIC, Fondation Marcel Merieux
17 rue Bourgelat
69002 Lyon, France
Tel.: (33) 72 73 79 04
Fax.: (33) 72 73 79 93