

Controlled Prospective Trial of Prednisolone and Cytotoxics in Progressive IgA Nephropathy

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Abstract. In a single-center, multiple-referral source study, 38 patients with progressive IgA nephropathy and controlled hypertension were randomized to treatment with prednisolone and cytotoxic agents, to therapy with low-dose cyclophosphamide then azathioprine, and to control groups. The follow-up period lasted 2 to 6 yr. Renal survival, as assessed by Kaplan-Meier analysis annually to 5 yr, showed significant preservation of function from 3 yr in the treatment group and 82, 82, 72, and 72% for 2, 3, 4, and 5 yr, respectively, compared with 68, 47, 26, and 6% in controls. Rate of loss of renal function, evaluated objectively by least-squares analyses of reciprocal serum creatinine, was reduced—and in one-third of the patients, arrested—during immunosuppressive treatment. Proteinuria, present in all patients at the time of entry into the trial, was reduced by treatment from 12 mo, compared with pretreatment levels or controls; erythrocyturia was reduced from 6 mo. Histologic activity and chronicity indexes were determined in renal biopsies performed at trial entry. Multivariate analysis

demonstrated that mesangial cell proliferation and matrix scores were highest in those patients with more rapidly progressive disease. No morphologic variable or residual renal function predicted response to immunosuppressive therapy at entry. Mean arterial pressures did not differ significantly between treatment and control groups. There was thus no explanation other than treatment for the improved outcome in patients who received immunosuppressive therapy. Morbidity attributable to treatment or to renal failure occurred in both groups; an audit showed that benefits of therapy outweighed expected or minor side effects of drugs in this population at risk of end-stage renal failure. Patients selected for moderately progressive IgA nephropathy benefit from treatment with prednisolone and cytotoxic agents; results are consistent with modulation of systemic immune response or nephritic injury, thus explaining improved outcome, and indicate that this therapy has an acceptably low risk of side effects.

IgA-related nephropathy (IgA-N) has become the most frequently detected glomerular disease in developed countries (1). Therapeutic intervention has been designed to modify disease expression in those with nephrotic syndrome or to arrest decline in renal function (2). In adults, and a minority of children with the closely associated disease Henoch-Schonlein purpura, treatment with corticosteroids has been used to suppress severe forms of refractory vasculitis. The acceptability of regimens requires a clear perspective of risk and benefit, with low toxicity a prerequisite for those with slowly progressive IgA-N. Untreated, actuarial kidney survival is 80 to 100% at 10 yr (3,4) and 70% at 20 yr, with less than half maintaining normal function (5). This slow deterioration, and the heterogeneity of groups studied, has contributed to the paucity of adequate prospective trials, and it is recognized that no therapy is established as beneficial (2,6–8).

Although benefit from fish oil is reported, 34% of the 106 patients at entry in the Mayo Collaborative study had normal

renal function. Heterogeneity weakening the power of the study also included the fact that 37% of entrants did not complete 2 yr, with only a small proportion participating for 3 yr or more, and late treatment introduced at 2 yr to some of the controls did not influence outcome (7). In contrast, a longer-term report (9) on this study suggested that further switching of patients from control to treatment group did benefit disease progression in those receiving fish oil, but reasons for selection of patients for change of status to starting treatment were unclear, and without reciprocation in a formalized crossover between groups, comparisons of outcome with controls places doubt on the value of this therapy.

A more recent controlled trial of short-term corticosteroids in 86 proteinuric patients (1 to 3.5 g/d) (8), many of whom had normal renal function at entry and who were also not selected for declining function, showed significant reduction in proteinuria. Patients with stable longer-term renal function thus entered both treatment and control groups, and the numbers of patients who developed significant impairment of function at 5 yr was small (14 *versus* 9). Also reducing the power of the analysis with respect to identifying effectiveness in preserving renal function was which patients should receive steroids—or, indeed, potentially more potent immunosuppressive therapy.

Hypertension that is not accelerated is nevertheless commonly associated with IgA-N of poor prognosis (2). It has proved difficult to establish the role of pressure as a significant

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factor causing secondary renal injury after that as a result of the immune-mediated glomerulonephritis. Morphologic changes found in hypertensive nephrosclerosis occur in severe IgA disease, and presumed flow disturbances and ischemia at the arteriolar level are intrinsically likely to accelerate loss of viable renal function. This issue—whether it contributes significantly to decline in function in this adverse prognosis group has proved difficult to address—further complicates the interpretation of nearly all published trials, particularly in those where treatment such as inclusion of corticosteroids itself predisposes the patients to increases in pressure.

In the study, we report design-strategy-restricted entry to a stratum of patients with impaired (serum creatinine greater than 130 $\mu\text{mol/L}$) and declining renal function, explicable only as a result of persisting immune-mediated glomerular injury; the study design was to provide for an outcome analysis within 5 yr. Patients were selected with moderately rapidly progressive disease, representing an important minority of IgA-N patients in whom serum creatinine was abnormal and rising by at least 15% in the year before entry. Reciprocal serum creatinine plot suggested end-stage renal failure within 5 yr. Preliminary study had shown renal biopsies of potential participants had global glomerulosclerosis exceeding 50% when serum creatinine was 250 $\mu\text{mol/L}$ or more, and entry was therefore empirically restricted to those with greater residual renal function. This strategy—evaluating the effects of immunosuppressive treatment of the patient subgroup with progressive IgA disease with a short window for entry—necessarily required referral sources from multiple centers to obtain a sufficient cohort within the study's planned timescale.

Materials and Methods

Subjects

The study was prospective, randomized, and performed in a single center. Thirty-eight patients referred from renal units in the northwest United Kingdom were eligible for trial entry from 1991 to 1996; 34 were men and 4 were women, and patients' ages ranged from 18 to 54 yr. Primary IgA-N was proven on renal biopsy by standard morphologic and immunohistochemical criteria, with negative serology for systemic lupus erythematosus. The study was approved by the ethics committee of the Central Manchester Healthcare Trust, and patients gave written consent. A withdrawal option was provided for the treatment group if significant side effects appeared during the first 2 yr. In addition, patients could exit the trial at 2 yr.

Controlled hypertension during the preceding 12 mo was a prerequisite for trial entry, and BP was maintained thereafter at levels of 160/90 mmHg or less. Patients were evaluated at a minimum of once every 3 mo throughout or monthly or more frequently in the 6 mo after trial entry; they were also evaluated if instability arose. Mean arterial pressures were evaluated throughout from clinical data. Patients included were specified as having isolated primary IgA-N. All patients having had serologic and plasma electrophoresis tests. Abnormalities permitting entry including raised total serum IgA only. All entrants were younger than 60 yr and did not have a history of known cardiac, liver, or other system pathology; this was done to exclude secondary forms of IgA-N. Previous accelerated hypertension was an exclusion criteria, as was related systemic disease (vasculitis), arteriopathic disease, and diabetes mellitus. In addition, women of reproductive age and patients who had previously received immunosup-

pressive or corticosteroid treatment were excluded. Angiotensin-converting enzyme inhibitors were permitted to be continued if patients were receiving these at the time of referral, but such therapy could not be subsequently altered; no patient who was provided AII-receptor blocking drugs was admitted to the study because of the paucity of data available on their effects on longer-term renal function in this setting at the time of trial design. Changes in BP of trial participants were controlled to pre-entry levels throughout; as first-line therapy, calcium antagonists and β -blockers were used.

Patients were randomized to a control group (no immunosuppression) or to a group that received treatment with prednisolone 40 mg/d (reduced to 10 mg/d by 2 yr) and cyclophosphamide 1.5 mg/kg per day (adjusted down to the nearest 50 mg) for the initial 3 mo, then azathioprine at the same dose continued for a minimum of 2 yr and, with patient consent, thereafter, until at least completion of assessment for the trial, up to 6 yr after entry. Duration of follow-up was 2 to 6 yr, with the low-dose immunosuppressive treatment unaltered, unless the patient reached end-stage renal failure. Clinical assessment of all patients occurred monthly for 6 mo after trial entry and once every 3 mo thereafter, with 24-h erythrocyte excretion estimated from microscopy of timed 2-h morning urine collections. Proteinuria and serum biochemistry were measured by standard methods.

Renal Biopsy Morphology Criteria

Renal biopsy, undertaken within 3 mo of trial entry, was examined by a single renal pathologist who was blinded to patient information; the biopsies were evaluated by criteria believed to be associated with prognosis (3,10–12). All biopsies were stained with hematoxylin and eosin, periodic acid–Schiff, and methenamine silver, and they were analyzed semiquantitatively for the following features: (1) percentage of glomeruli showing global sclerosis; (2) extent of segmental and global glomerulosclerosis (0 = no sclerosis, 1 = 1 to 24%, 2 = 25 to 50%, 3 = more than 50% of glomerular area sclerosed; each glomerulus was scored individually, and the mean score for all glomeruli in the biopsy was calculated); (3) severity of mesangial cell proliferation (0 = no proliferation, 1 = mild proliferation, with 3 to 4 mesangial cells per peripheral lobule, 2 = segmental severe proliferation, with more than 4 mesangial cells per peripheral lobule, 3 = global severe proliferation; each glomerulus was scored individually and the mean scores calculated for all nonsclerosed glomeruli); (4) severity of increase in mesangial matrix (0 = no increase in matrix, 1 = mild increase in mesangial matrix, 2 = segmental marked increase in mesangial matrix, defined by the width of the mesangial interspace between capillaries exceeding 3 mesangial cells, 3 = global marked increase in mesangial matrix; each glomerulus was scored individually and the mean scores calculated for all nonsclerosed glomeruli); (5) extent of interstitial fibrosis and chronic inflammation (0 = no fibrosis or inflammation, 1 = 1 to 24%, 2 = 25 to 50%, 3 = more than 50% of biopsy area showing fibrosis or inflammation); (6) extent of tubular atrophy (0 = no atrophy, 1 = 1 to 24%, 2 = 25 to 50%, 3 = more than 50% of tubules atrophic); (7) severity of arteriosclerosis or arteriolar hyalinosis (0 = no hyalinosis, 1 = mild hyaline thickening of at least 1 arteriole, 2 = severe hyaline thickening in at least 1 arteriole, 3 = severe hyaline thickening in many arterioles); (8) severity of arteriosclerosis (0 = no sclerosis, 1 = 1 to 24%, 2 = 25 to 50%, 3 = more than 50% luminal narrowing by fibroelastic intimal thickening in the most severely affected vessel).

A biopsy that contained eight or more glomeruli was considered to be adequate for histologic analysis.

Statistical Analyses

Renal survival, assessed via Kaplan-Meier functions, were compared by log-rank and Tarone-Ware tests. The method of Wentworth (13) was used for assessing trial suitability by objective least-squares fit estimates from reciprocal serum creatinine plots and for assessment from 3 mo after trial entry. Clinical variables were compared by Wilcoxon-Mann-Whitney *U* test, *t* test, and Pearson's correlation coefficient, and morphologic data were analyzed by Kolmogorov-Smirnov two-tailed test.

Results

Patients fulfilling the trial entry criteria recruited from eight participating renal units were predominantly male (90%), and most were younger than 45 yr of age. Analysis of the treatment (19 patients) and control groups (19 subjects) (Figure 1) showed that cumulative renal survival after 2 yr in the treatment group was significantly improved ($P < 0.05$, log rank); at 5 yr, functional renal preservation was highly significant ($P = 0.006$, log rank; $P = 0.036$, Tarone-Ware). These findings are notwithstanding the effects of 3 patients who withdrew from the treatment group during year 1 for reasons of azathioprine-induced marrow suppression ($n = 1$); secondary diabetes mellitus ($n = 1$); and unrelated injury ($n = 1$). These withdrawals incurred analysis events, thus skewing treatment group data toward lower survival figures. One patient in the treatment group developed pulmonary tuberculosis, to which there was a potential occupational risk of exposure, and was successfully treated. No other side effects of treatment occurred. One patient in each group died after they exited the trial; complications of end-stage renal failure and dialysis were the causes. One patient in the control group experienced a perforated colonic diverticulum, which precipitated acute chronic renal failure.

No patient elected to exit the trial at 2 yr, as offered by the protocol. All patients but one in the control group who received standard supportive treatment only reached end-stage renal failure by 5 yr after entry, as anticipated, with 100% failing by

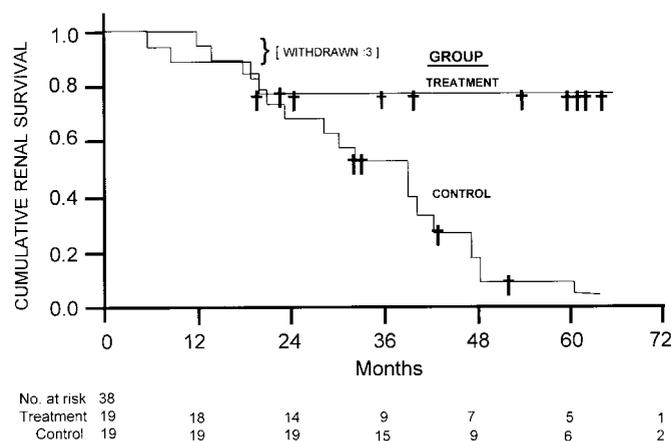


Figure 1. Kaplan-Meier survival functions for progressive IgA-related nephropathy for treatment and control groups. Preservation of function was significant after 2 yr ($P = 0.006$, log rank; $P = 0.036$, Tarone-Ware; †, censored—i.e., not incurring event).

year 6. There was a marked linearity of decline in loss of GFR, assessed objectively by reciprocal serum creatinine plots, the Wentworth routine least-squares analysis showing variability from linearity of less than 10% (13,14) throughout the decline in function of the control group, and similarly in the 2 phases of the treatment group, before and from 3 mo after entry. Rate of decline data for the two groups (Figure 2) is shown for comparative purposes and to provide a template for evaluation of suitability for future patient treatment, but these data were not used as a factor for renal survival by event analysis. Pretreatment loss of function rates did not differ between the groups; mean function loss was more than fourfold lower in the treatment group. However, there was substantial heterogeneity of response apparent from treatment (Figure 3), ranging from complete stability of function to 5 yr to no discernible benefit.

Treatment reduced proteinuria from 12 mo and was sustained in the treatment group compared with pretrial values, or compared with controls, who showed no significant changes throughout (Figure 4). Likewise, erythrocyturia was reduced from 6 mo in the treatment group (Figure 5). Both urinalysis parameters were comparable between groups, as were mean rates of loss of function, before trial entry.

Renal biopsy data, summarized in Figure 6, showed that there was no significant difference in histologic parameters between the two groups, with the exception of arteriosclerosis, which was more severe in the treatment group, which had the better outcome. The glomerular morphology in all patients was a mesangial proliferative glomerulonephritis with focal endocapillary proliferation and focal segmental and global glomerulosclerosis. Endocapillary proliferation, where present, was segmental and associated with tuft adhesions, small foci of extracapillary proliferation, or both. None of the biopsies showed a true crescentic glomerulonephritis. The extent of endocapillary proliferation correlated with the severity of mesangial cell proliferation ($P < 0.05$). All biopsies showed varying degrees of interstitial inflammation and fibrosis, with the extent of mononuclear cell infiltration correlating with fibrosis ($P < 0.05$).

Patients who had more rapidly progressing disease at the time of entry, defined by the slope of the reciprocal serum

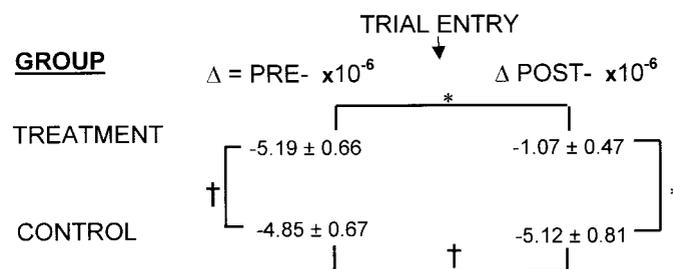


Figure 2. Rate of decline of renal function before and after trial entry for treatment and control groups. The mean rate of decline was reduced more than fourfold in the treatment group (mean \pm SEM; *, $P < 0.005$, *t* test; †, $P = \text{NS}$; units are $\Delta = \text{L} \cdot \mu\text{mol}^{-1} \cdot \text{d}^{-1}$). End-stage failure in 5 yr implies renal function loss, $\Delta \geq -4.9 \times 10^{-6} \text{ L} \cdot \mu\text{mol}^{-1} \cdot \text{d}^{-1}$.

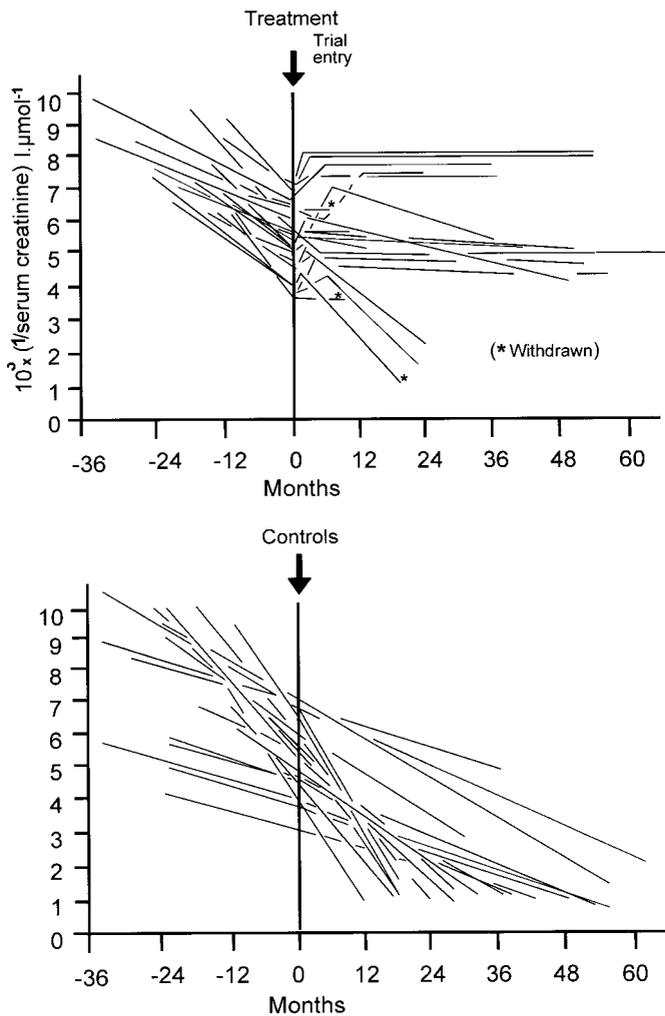


Figure 3. Patient data reciprocal serum creatinine plots. Lines are least-squares analyses of data.

creatinine plot, were found to have more severe mesangial cell proliferation ($P = 0.018$) (Figure 7) and a greater increase in mesangial matrix ($P < 0.05$). The severity of other histologic variables did not correlate with rate of decline of renal function.

Mean arterial pressure data are depicted once every 3 mo for

2 yr before and after entry, then every 6 mo thereafter (Figure 8). More than 98% of pressure readings showed no significant difference between the means of control and treatment groups, although one evaluation, 48 mo into the trial, was higher in the control group.

Multivariate analysis of all clinical data, including serum creatinine at entry and morphologic data, did not identify any variable that permitted identification of patients who subsequently responded positively or otherwise to treatment. Response for the purposes of this question was defined as a reduction in the average rate of decline of the reciprocal serum creatinine plot, pre- versus post-trial entry, by twofold or more; in all cases, this exceeded 2 SD of the least-squares value of deviation from linearity obtained from reciprocal serum creatinine analysis.

Discussion

In this stratum of IgA-N patients, all displayed clinical criteria known to predispose people to disease progression (15), characterized by impaired renal function, hypertension, absence of macroscopic hematuria, and heavy proteinuria. Selection for rapidity of renal function loss defined this minority of IgA disease patients for trial entry, with actuarial kidney loss more generally being approximately 10% per decade for all IgA-N patients (reviewed in [2]). In evaluating acceptability of therapeutic regimens for IgA-N, a clear perspective of relative risk and benefit is essential; low toxicity is a prerequisite for those with minimal disease progression.

The illnesses experienced in the control and treatment groups were analyzed in detail. One patient in each group was likely to have had serious illness arising as an unrelated event: the acute perforation of a diverticulum, precipitating acute irreversible renal failure and the need for intensive care, in controls as random; the development of pulmonary tuberculosis in a young white doctor-in-training exposed to acutely ill patients in an emergency department inner-city hospital, was considered to be occupationally acquired. Two treatment group patients, one with azathioprine-induced marrow suppression and the other with secondary diabetes mellitus, exited the trial. Both recovered fully, and these events of morbidity were considered likely to have arisen in due course on exposure to these drugs if renal transplantation were undertaken at end-stage renal failure. The deaths of two patients, one in each group, occurred after the patients had reached end-stage renal failure and after they had left the study, and they were clearly attributable to complications of dialysis or transplantation.

Patients entering this study thus were exposed to risks comparable to those that they would almost inevitably experience during subsequent dialysis and transplantation if disease progressed when the immunosuppressive drugs of this trial or when similar drugs were used. The immunosuppressive therapy used in our study design, although at low dose, may not fulfill the risk-benefit requirement incorporated in our strategy for patients with slower progression disease who are at lesser risk of early renal failure.

The 5-yr renal survival of 38 patients in this study showed that in the treatment group, 72% of patients, compared with 5% of controls, had functioning kidneys. This outcome analysis is

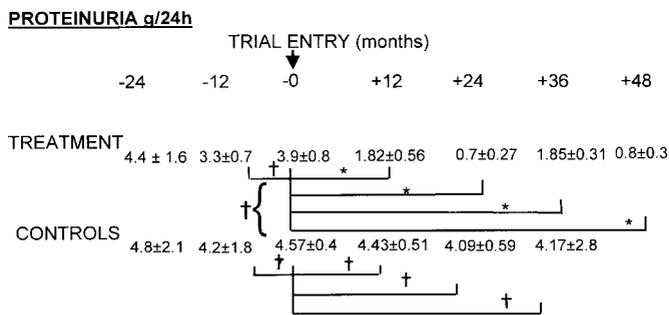


Figure 4. Trial proteinuria data. Significant reductions in the treatment group were consistent from 12 mo after trial entry (mean ± SEM; *, $P < 0.02$; †, $P = NS$; Wilcoxon-Mann-Whitney test).

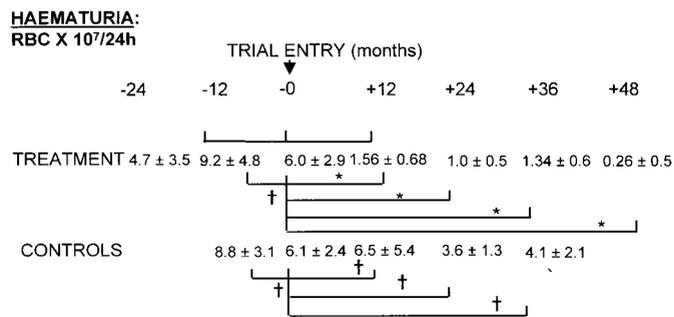


Figure 5. Erythrocyturia reduced from 6 mo in the treatment group (mean ± SEM; *, $P < 0.02$; †, $P = NS$; Wilcoxon-Mann-Whitney test).

independent of assumptions about serum creatinine-related functions. This critical analysis of organ loss includes the effect of three patients' withdrawal from the treatment group. End-stage renal failure occurring at a high frequency in controls was expected from the study design; this clinically homogeneous cohort was selected for more severe disease. In contrast, of 86 patients entered into an Italian multicenter study of short-term steroid therapy who had normal renal function (creatinine less than 130 $\mu\text{mol/L}$), only 23 developed impaired function in treatment and control groups together, and there was a 93% renal survival, with 80% maintaining normal renal function in the control group alone (8). The small number of patients apparently benefiting from treatment was thus balanced against the exposure of the majority receiving treatment whose disease did not merit it. In contrast, in our study, the use of steroids with cytotoxic drugs was restricted to those at the highest risk of renal failure.

Modification of urinalysis, hematuria, and proteinuria in the treatment group was a consistent and predictable feature. Erythrocyturia was suppressed after 6 mo and proteinuria after 12 mo of treatment, compared with pretreatment levels and compared with controls. Although these findings provide only circumstantial evidence for suppression of nephritic activity and healing of glomerular protein leak, their consistency and magnitude—20-fold and 5-fold, respectively, compared with

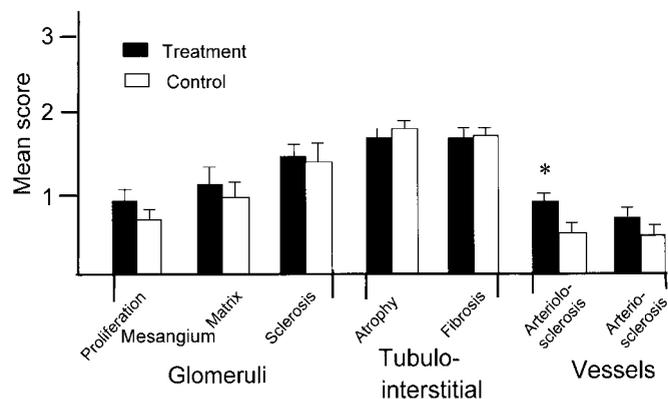


Figure 6. Histologic parameters in renal biopsies at trial entry (mean ± SEM; *, $P = 0.04$, Kolmogorov-Smirnov 2-tailed test).

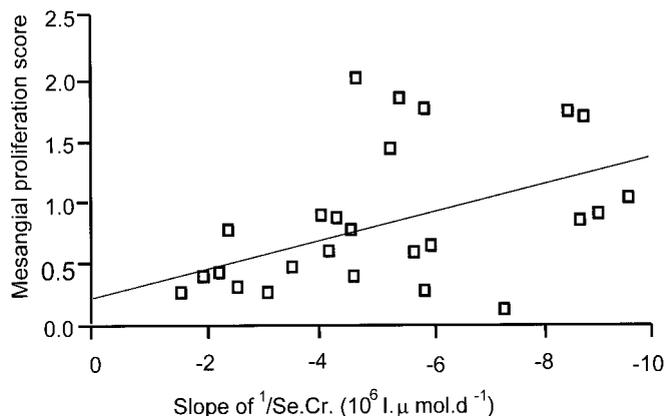


Figure 7. Disease progression rate versus biopsy morphology for all patients. Mesangial proliferation score associated with more rapid loss of GFR in both groups ($P = 0.018$, Pearson's coefficient).

little or no reduction in the control group—is a powerful argument suggesting that glomerular injury and inflammation were reduced in the treatment group.

Renal biopsy data showed significant glomerular injury in all trial entrants. None of the patients in this study showed glomerular crescents in the biopsies performed at entry into the study. The absence of significant differences between morphologic features of patients in either group provides evidence of matching for adverse features. The unexpected increased frequency of arterio-sclerosis in the treatment group with the improved outcome is supportive evidence that mismatch of severity of renal injury at trial entry was not the explanation for the improved outcome in those treated. Detailed additional morphologic analysis, including mesangial cell proliferation, did not provide any independent histologic feature that would assist in defining the potentially responsive subgroup of patients with progressive disease.

The data (Figure 7) do reveal consistency in the positive association between mesangial cell proliferation with the rapidity of disease progression in both groups, but the severity of proliferation was not associated with treatment responsiveness. The marked heterogeneity of response to immunosuppressive therapy was also not explicable by any other morphologic variables. Features such as evidence of interstitial inflammation, ostensibly responsive to the effects of corticosteroids, did not correlate with outcome, nor did they define the subgroup of patients who clearly responded to immunosuppressive therapy and who were responsible for improved overall renal survival in the treatment group. Although there are potential associations of responsiveness with systemic variables describing immune system dysfunction (assessed in a separate study), they did not form part of this clinical trial protocol.

Mean arterial pressures did not differ between control and treatment groups for more than 98% of readings in the 2 yr of pre-entry assessment and the first 4 yr after trial entry. A single point of analysis at 48 mo showed significantly higher control group pressures, attributable to 2 patients in the control group who displayed unstable hypertension when end-stage renal failure was inevitable and imminent (serum creatinine exceed-

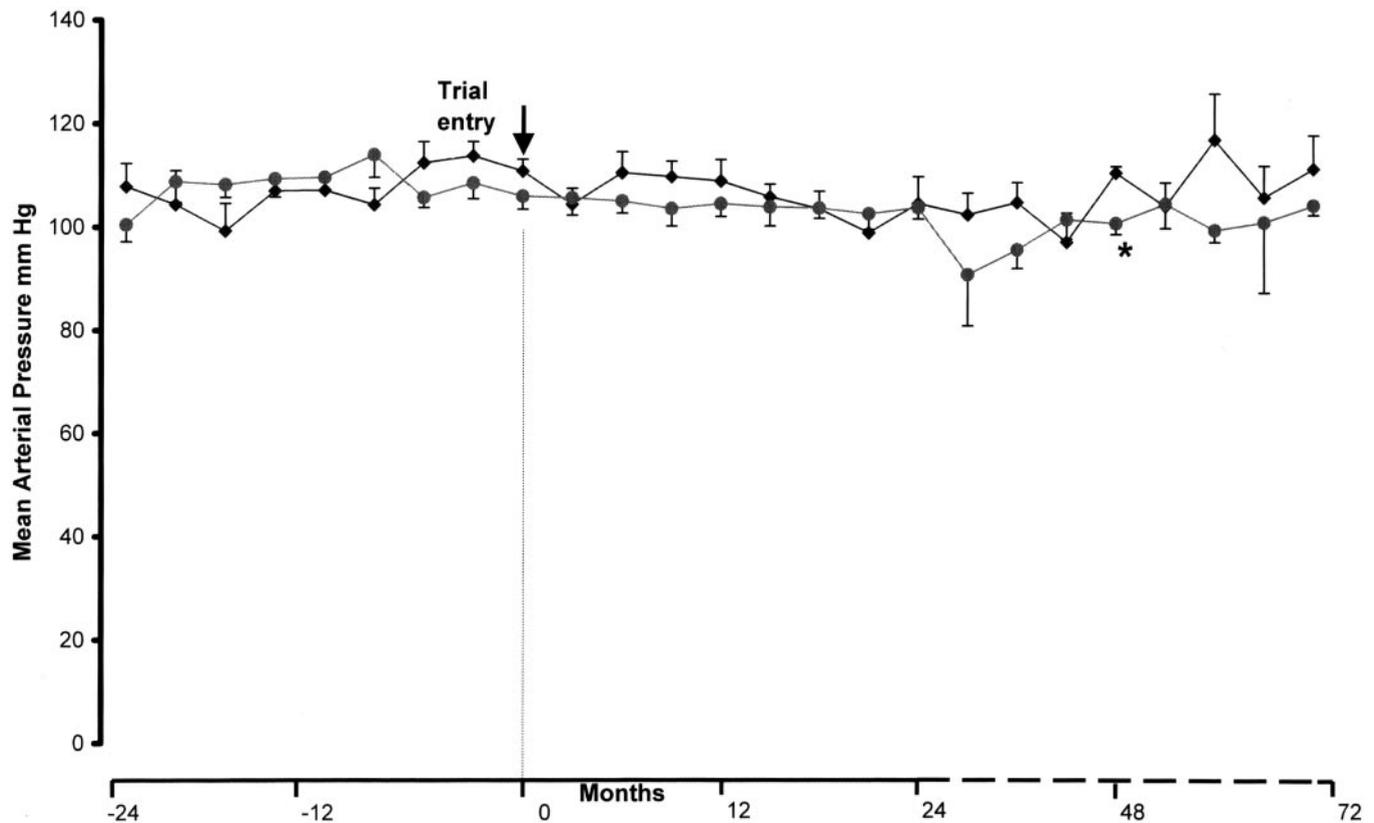


Figure 8. Mean arterial pressures \pm SEM for control (◆) and treatment (●) groups during pretrial assessment before randomization and during the IgA nephropathy trial ($P = \text{NS}$ throughout, except *, $P = 0.04$ at +48 mo, t or Wilcoxon-Mann-Whitney tests).

ing 500 $\mu\text{mol/L}$ before instability in pressures). This could not have influenced the outcome analysis, however, because cumulative renal survival was significantly better in the treatment group earlier, after 2 yr, group survival curves continued to diverge before and after this point. In each group, five patients received angiotensin-converting enzyme inhibitors, which, according to protocol, were unaltered throughout the trial.

Hypertension is a recognized adverse prognostic feature, together with heavy proteinuria, absence of macroscopic hematuria, and impaired function at presentation, in most series describing the natural history of IgA disease (2). Its significance in causing secondary, additional renal injury after that as a result of severe immune-mediated glomerulonephritis, or whether it is primarily responsible for declining function in this adverse prognosis group, has proved controversial. The data presented in this study, with concordance of mean arterial pressures in the immunosuppressed and control groups, underscore the conclusion that hypertension is a secondary event, and when controlled, it does not contribute to decline in renal function due to immune-mediated injury.

Emerging concepts in the pathogenesis of IgA-N provided the rationale for treatment of progressive disease with prednisolone and cyclophosphamide, then azathioprine. There are certain parallels to be drawn between the pathogenesis of IgA disease and lupus nephritis, with selective activation of monocyte-derived and intrarenal cytokine systems, autoimmune

events occurring with both IgA and IgG isotypes, and marrow B cell activation (2). The efficacy of steroid therapy, particularly in combination with cytotoxics in lupus nephritis (16), suggested potential benefit of this therapy in IgA disease. The choice of cyclophosphamide for initial therapy was not only enhanced by its arguable efficacy over azathioprine in preserving renal function in systemic lupus erythematosus (17), but also by its intrinsic ability to abrogate or reduce B cell responses, including immunogen-induced, gut-associated lymphoid tissue derived by IgA in experimental systems (18). Although the pathogenesis of primary IgA-N is no longer widely accepted as a form of so-called mucosal serum sickness, direct deposition of mucosal surface-derived immune complexes in glomeruli, microbial, and other antigenic challenge at mucosa undoubtedly provides a stimulus for marrow-derived immune system reactants, contributing to disease pathogenesis and glomerular injury.

Our study did not attempt to answer the question as to whether patients with extensive redundancy of renal tissue (serum creatinine $> 25 \mu\text{mol/L}$) might benefit from late introduction of immunosuppressive drugs. Three patients, studied before the final trial design had been established, started treatment with serum creatinines greater than 250 $\mu\text{mol/L}$ but failed to respond, as assessed by lack of apparent effect on the slope of reciprocal of serum creatinine. It was believed that the effects of hyperfiltration in such patients with extensive histologic evidence of renal scar-

ring—with the percentage of glomeruli sclerosed exceeding 50% and the remainder showing advanced changes—would make a poor population to evaluate the effects of drugs designed to modulate immune response and functionally important inflammatory nephritis, and so these patients were excluded from the final trial design. We emphasize that their numbers were small, and so they might by chance have been in the unresponsive category of patient in any event. From first principles, it would appear that patients with such advanced disease are an unrewarding group to treat and at higher risk of morbidity from immunosuppressives, and so they were not included.

Retrospective analysis of all patients who received prednisolone and cyclophosphamide then azathioprine—that is, including these three anecdotal, preliminary patients studied—certainly supports the contention that the probability of response to immunosuppressives is inversely related to serum creatinine at the start of treatment. Formal analysis of the trial patients only for this correlation as part of the multivariate analysis to identify the characteristics of responders and nonresponders, however, showed that this suggested association did not reach statistical significance. We propose, therefore, that our experience suggests that early treatment with immunosuppressives, with serum creatinine levels abnormal but lowest at commencement of therapy, confers the best chance of success.

The advisability of continuing long-term, low-dose immunosuppression, as prednisolone 5 to 7.5 mg/d and azathioprine after 5 yr in patients who have avoided renal failure, has not been answered by this trial. The design was not intended to address this question, nor was the relative importance of each of the treatment drugs used assessed; the latter question could only be answered by a randomized withdrawal of treatment within the successfully treated group. Two patients elected to discontinue treatment 7 yr after starting, and both exhibited relapses in their stable renal status. One relapsed to a nephrotic state, and the other relapsed to significant proteinuria and declining function. Both reverted to their stable state when low-dose therapy was reintroduced. These anecdotes suggest the efficacy of long-term treatment in those who have initially responded to such therapy.

Increasing evidence now supports the judicious introduction of steroids, with cytotoxic immunosuppressives in patients with severe progressive IgA-N as a viable and effective treatment able to reduce the frequency and inevitability of end-stage renal failure. The impact on renal failure support program is potentially significant, and future studies may refine acceptable low-risk use of immunosuppression on the widest spectrum of IgA disease.

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