Treatment of progressive renal failure and nephrotic syndrome with azathioprine and prednisolone

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Summary

Four patients with idiopathic membranous glomerulonephritis, heavy proteinuria and progressive renal failure received azathioprine and prednisolone. Renal function improved in all four and proteinuria declined sharply in three. We suggest that treatment with azathioprine and prednisolone may be of benefit in this form of idiopathic membranous glomerulonephritis.

Keywords: membranous glomerulonephritis, azathioprine, prednisolone, renal failure

The role of immunosuppressive therapy in the treatment of idiopathic membranous glomerulonephritis remains controversial. Most patients do well with conservative management, but an important minority develop severe progressive renal failure leading to dialysis dependence.¹ This has, in all probability, had a confounding effect upon the analysis of clinical trials of immunosuppressive therapy which have included unselected patients with the condition.

Clear criteria for deciding at an early stage whether an individual patient is destined to do badly are not available. Persistent heavy proteinuria combined with a progressive severe decline in excretory function is indicative of poor prognosis.^{2–5} In such patients, a progressive clinical course is the rule.²

Most studies of treatment have employed cyclophosphamide or chlorambucil alone or in combination with corticosteroid therapy. A recent meta-analysis⁶ of prospective controlled studies employing these agents provided convincing evidence of benefit in terms of increased probability of complete or partial resolution of proteinuria. Controlled studies of the use of azathioprine with or without prednisolone are unavailable, but the uncontrolled report of Williams and Bone⁷ is suggestive of benefit in patients with heavy proteinuria and progressive renal impairment. We have only employed azathioprine and prednisolone in patients with idiopathic membranous glomerulonephritis in this category, on the assumption that the risk of side-effects of treatment are likely far to outweigh any possible benefit in patients with less severe illness. We report our experience of four treated and three untreated patients

under our care who fulfilled the necessary criteria.

Case reports

Seven patients (all male) with renal biopsy-proven idiopathic membranous glomerulonephritis, nephrotic range proteinuria and progressive severe renal failure seen since 1980 in whom adequate follow-up data were available are reported. Patients were identified from histopathological records and clinical notes. Progressive severe renal failure in treated patients was defined as a rise in serum creatinine concentration of 90 $\mu\text{mol/l}$ or more to reach a concentration of 300 $\mu\text{mol/l}$ or more over an observation period of 12 months.

Treatment was then commenced with azathioprine, 100 mg daily for 12 months and prednisolone, 20–40 mg daily, the latter being reduced to 10–20 mg daily at 12 months. In untreated patients, a serum creatinine similar to that of one of the treated group was chosen and taken to be that obtained when a decision not to treat had been made. Observations were then recorded from 12 months before and 12 months after this. Decisions as to whether to treat or not treat were a matter of individual physician preference. At presentation, no patient had clinical or serological evidence of systemic lupus erythematosus, all were hepatitis B surface antigen negative and none had evidence of malignancy. No patient had taken a drug known to cause membranous nephropathy.

Two of the four treated patients received an angiotensin-converting enzyme (ACE) inhibitor (captopril or enalapril). In one patient, this was started after azathioprine and prednisolone and after serum creatinine had begun to decline. Urinary protein loss declined following initiation of the ACE inhibitor. In the other patient, the ACE inhibitor was commenced one year before azathioprine and prednisolone treatment, with no apparent effect upon serum creatinine or urinary protein loss.

Serum creatinine concentration and urinary protein output in the four treated patients before and after 12 months of treatment are given in table 1. Similar data in the three untreated patients are given in table 2. A decline in serum creatinine concentration and a trend towards a fall in urinary protein output was seen in treated patients. This improvement was sustained with long-term treatment at

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Table 1 Effect of treatment for 12 months on serum creatinine concentration and urinary protein output

Serum creatinine ($\mu\text{mol/l}$)			Proteinuria (g/24 h)		
-1 year	0	+1 year	-1 year	0	+1 year
300	410	250	14.6	15.6	3.9*
220	310	180	10.5	6.0	8.0
200	410	280	16.8	10.3	4.8*
260	370	250	NM	12.3	2.4

NM=not measured; *also received treatment with an ACE inhibitor

Table 2 Untreated patients. Observations over 24-month period

Serum creatinine ($\mu\text{mol/l}$)			Proteinuria (g/24 h)		
-1 year	0	+1 year	-1 year	0	+1 year
280	380	630	NM	NM	NM
100	320	>1000	12.8	17.0	on dialysis
330	430	630	4.0	NM	NM

NM=not measured

lower dosage levels of azathioprine and prednisolone, renal function having remained stable in the treated patients over several years. All three untreated patients progressed to end-stage renal failure.

Side-effects of treatment within one year were few. One patient developed a cataract, possibly attributable to steroid therapy, requiring operation.

Discussion

The place of immunosuppressive therapy in general and of azathioprine and prednisolone in particular in membranous nephropathy remains uncertain, despite widespread study and despite the findings reported here. The main reason for this lies in the fact that the majority of patients with the condition are destined to do well, at least for several years. The need is for prospective controlled double-blind trials in patients identified as having a poor prognosis by the presence of nephrotic range proteinuria and a defined deterioration in excretory function before commencement of the study.

Our findings may be criticised on several

Learning points

- the role of immunosuppressive therapy in idiopathic membranous nephropathy is unclear
- most patients do well without treatment, but those with heavy proteinuria and progressive renal failure do badly
- azathioprine and prednisolone treatment may be beneficial in this subgroup of patients

counts: the number of patients involved is small, the study is retrospective and allocation to treatment or no-treatment groups was based upon individual physician preference rather than by randomisation. Nevertheless, all patients fulfilling the criteria and seen at our institution in whom adequate records are available have been included and we believe our observations lend strong support to the notion that azathioprine, with or without prednisolone, is of benefit. Spontaneous recovery of renal function in idiopathic membranous glomerulonephritis, once a progressive and serious decline has become established, appears to be very unusual, whereas all four treated patients improved following treatment. Moreover the three untreated patients progressed inexorably to end-stage renal failure. We consider it unlikely that improvement in renal function can be attributed to concomitant ACE-inhibitor treatment in the two patients so treated.

The treatment regimen we have employed is simple and familiar to nephrologists. Side-effects of such treatment cannot be ignored but are also familiar and are of an acceptable order of magnitude when set against the prospect of development of end-stage renal failure. They are probably less severe than those to be expected with regimens employing, for example, cyclophosphamide or chlorambucil.

We believe a reasonable current policy is to reserve azathioprine and prednisolone treatment for patients with significant deterioration in renal function for which causes other than progression of the underlying membranous nephropathy can be excluded. A final conclusion as to the place of this regimen in treatment must, however, await the results of a properly conducted controlled trial.

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