

# Controlled trial of azathioprine in the nephrotic syndrome secondary to idiopathic membranous glomerulonephritis

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In a controlled double-blind trial five patients with the nephrotic syndrome due to idiopathic membranous glomerulonephritis received azathioprine, 2.5 mg/kg·d, while four others received placebo. After 1 year of treatment there was no significant difference between the two groups with regard to the changes in leukocyte count, values for hemoglobin, serum creatinine, blood urea nitrogen or serum albumin, 24-hour excretion of protein in the urine, or creatinine clearance. In this study azathioprine appeared not to be useful in the treatment of idiopathic membranous glomerulonephritis.

Dans une étude contrôlée à double-insu cinq patients souffrant de syndrome néphrotique dû à une glomérulonéphrite idiopathique membraneuse ont reçu 2.5 mg/kg d'azathioprine par jour, alors que quatre autres patients ont reçu un placebo. Après 1 an de traitement aucune différence significative n'a été observée entre les deux groupes quant aux changements dans le décompte des leucocytes, les mesures de l'hémoglobine, la créatinémie, l'azote uréique du sang ou l'albuminémie, l'excrétion urinaire des protéines de 24 heures, ou la clearance de la créatinine. Dans cette étude l'azathioprine n'a pas semblé contribuer de façon utile au traitement de la glomérulonéphrite idiopathique membraneuse.

Membranous glomerulonephritis is a glomerular lesion characterized by deposits of antigen-antibody complexes in the subepithelial side of the glomerular capillary basement membrane.<sup>1,2</sup> In most cases the antigens have not been identified.<sup>3</sup> Because of its possible immunologic cause, this condition has been treated with immunosuppressive agents. However, controlled studies of treatment with steroids alone,<sup>4</sup> steroids and azathioprine,<sup>5</sup> and cyclophospham-

ide alone<sup>6</sup> have failed to show any benefit. The trial of steroids and azathioprine, however, lasted only a few months.

This report documents the results of 1 year of treatment with either azathioprine or placebo in nine patients with membranous glomerulonephritis and the nephrotic syndrome.

## Patients and methods

For a patient to be eligible for entry into the study, his or her renal biopsy, which had to have been performed during the preceding 6 months, had to show changes of membranous glomerulonephritis by light and electron microscopy and immunofluorescent staining; the 24-hour protein excretion had to exceed 3 g/d on three occasions over a maximum period of 6 weeks; and the 24-hour creatinine clearance had to average more than 50 ml/min·1.73 m<sup>2</sup> on three occasions over a 6-week period. The same immunofluorescent serum was used by all four centres — Calgary, Edmonton, Vancouver and Winnipeg — participating in the study. One pathologist in each centre made the initial diagnosis, but at the end of the study the four pathologists collaborated in a review of all cases. The histologic appearance was staged by the classification of Ehrenreich and Churg.<sup>1</sup> There was complete agreement on the staging in each case.

The membranous glomerulonephritis had to be idiopathic. When the condition was secondary to such diseases as acute streptococcal glomerulonephritis, lupus erythematosus, diabetes, syphilis, malaria, intestinal carcinoma, lymphoma, amyloidosis or drug-induced nephropathy the patient was excluded. Patients with evidence of extensive old tuberculosis or active tuberculosis were excluded, as were pregnant patients.

Patients were required to have received no azathioprine, cyclophosphamide or nitrogen mustard for at least 1 year before entry into the trial, and no steroids for at least 4 months. The patients had to be between the ages of 18 and 70 years. If the diastolic blood pressure persistently exceeded 95 mm Hg the patient was treated with antihypertensive agents.

Seven physicians from the four centres treated nine patients. The trial was controlled and double-blind, with patients randomly assigned by the

closed-envelope technique to either the azathioprine (five patients) or the placebo (four patients) group. The null hypothesis that there was no difference between the two groups was adopted. The azathioprine group received 2.5 mg/kg·d of the drug (in 50-mg tablets) in a once-a-day dosage; the placebo group received a similar number of placebo tablets. Only the pharmacist knew which tablets were azathioprine and which were placebo. The patients continued taking azathioprine or placebo for 1 year.

Leukocyte, differential and platelet counts, concentrations of hemoglobin, blood urea nitrogen (BUN), serum creatinine, serum glutamic oxaloacetic transaminase (SGOT) and serum bilirubin, serum protein electrophoresis and 24-hour excretion of protein in the urine were monitored every 2 to 6 weeks throughout the year. Comparisons were made between values before treatment and those at the end of the year for both groups.

## Results

In the azathioprine group the 24-hour excretion of protein in the urine had decreased significantly ( $P < 0.05$ ) after 1 year of treatment (Tables I and II). None of the other values had changed significantly.

In the placebo group the BUN had increased significantly ( $P < 0.05$ ) after 1 year of treatment. None of the other values had changed significantly.

Comparisons made between the two groups by analysis of covariance (using the pretreatment values as the covariate) showed no significant differences in any of the values.

In no instance did the leukocyte count decrease to less than  $3.0 \times 10^9/l$  or the platelet count to less than  $120 \times 10^9/l$  after treatment. There were no instances of hepatic damage as evidenced by elevations in the SGOT or serum bilirubin values.

## Discussion

This study failed to demonstrate any difference between the results of azathioprine and placebo treatment for 1 year in membranous glomerulonephritis.

In only one other controlled study has azathioprine been used to treat membranous glomerulonephritis.<sup>5</sup> In

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Table I—Characteristics of patients with membranous glomerulonephritis before treatment with azathioprine or placebo

Patient group and no.	Histologic stage <sup>1</sup>	Age (yr)	Sex	BP (mm Hg)	Hb (g/dl)	WBC (x 10 <sup>9</sup> /l)	Serum creatinine (mg/dl)	BUN (mg/dl)	Serum albumin (g/dl)	24-hour urine protein excretion (g/d)	Creatinine clearance (ml/min·1.73 m <sup>2</sup> )
<b>Azathioprine</b>											
1	2	27	M	140/100	13.5	5.9	1.3	22	1.9	20.4	65
2	2	66	M	122/82	12.6	4.6	1.8	38	3.1	10.9	70
3	2	37	F	110/70	15.0	6.1	0.9	14	2.8	7.2	88
4	2	40	M	130/84	13.4	4.9	0.8	12	2.4	11.7	158
5	3	36	F	110/90	12.7	5.8	0.9	18	2.0	10.6	92
Mean		41		122/85	13.4	5.5	1.1	21	2.4	12.2	95
SD		15		13.0/11.0	1.0	0.7	0.4	10	0.5	4.9	37
<b>Placebo</b>											
6	1	26	M	124/80	11.0	6.7	1.9	22	2.2	15.0	50
7	2	34	M	130/80	13.5	7.6	1.3	13	2.4	13.2	80
8	2	62	F	120/80	12.8	5.7	0.8	16	2.5	3.3	101
9	2	58	M	140/78	12.4	7.7	1.9	18	2.8	4.7	64
Mean		45		129/80	12.4	6.9	1.5	17	2.5	9.1	74
SD		18		8.7/1.0	1.1	0.9	0.5	4	0.3	5.9	22

Table II—Characteristics after 1 year of treatment

Patient group and no.	BP (mm Hg)	Hb (g/dl)	WBC (x 10 <sup>9</sup> /l)	Serum creatinine (mg/dl)	BUN (mg/dl)	Serum albumin (g/dl)	24-hour urine protein excretion (g/d)	Creatinine clearance (ml/min·1.73 m <sup>2</sup> )
<b>Azathioprine</b>								
1	148/110	9.6	4.3	3.5	39	2.2	3.8	24
2	124/82	9.9	6.9	2.7	41	2.5	10.3	49
3	130/76	12.9	5.0	0.9	17	4.2	3.8	118
4	130/75	14.5	6.1	0.8	13	2.8	3.6	160
5	112/76	12.5	5.8	1.2	19	3.5	4.7	86
Mean	129/84	11.9	5.6	1.8	26	3.0	5.2	87
SD	13.0/14.9	2.1	1.0	1.2	13	0.8	2.9	54
<b>Placebo</b>								
6	150/82	9.9	7.8	4.7	26	2.2	7.5	25
7	130/75	11.5	10.5	1.9	25	3.3	3.7	48
8	135/80	12.6	6.6	1.0	19	3.9	0.3	73
9	165/94	12.4	7.4	1.8	33	2.9	4.9	68
Mean	145/83	11.6	8.1	2.4	26	3.1	4.1	54
SD	15.8/8.1	1.2	1.7	1.6	5.7	0.7	3.0	22

that study five patients received, for 2 to 6 months, azathioprine, 2.5 mg/kg·d, and prednisone, 20 mg/d for adults and 0.5 mg/kg·d for children. Nine patients received no treatment. No significant differences between the two groups in values for creatinine clearance, proteinuria, plasma albumin or plasma urea were detected during the study.

In another controlled study<sup>4</sup> eight patients with membranous glomerulonephritis received prednisone, 20 to 30 mg/d, for not less than 6 months. There were no significant differences between this group and six untreated patients.

In a third controlled study<sup>6</sup> 11 patients with membranous glomerulonephritis received cyclophosphamide orally, 1.5 to 2.5 mg/kg·d for 1 year, while 11 others received no drug. The

treatment did not have a favourable effect on proteinuria, renal function or morphologic aspects of the glomerular lesion.

Although favourable effects have been reported in some cases of membranous glomerulonephritis treated with a combination of anticoagulants, platelet inhibitors and immunosuppressive agents,<sup>7</sup> these results may have been due to the natural course of this disease. Controlled clinical trials of this combination of agents in membranous glomerulonephritis have not been reported.

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