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The effects of azathioprine and prednisolone on T- and B-lymphocytes in patients with lupus nephritis and chronic glomerulonephritis

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Abstract. The effects of long-term treatment with azathioprine and prednisolone on T- and B-lymphocytes were studied in 52 patients with lupus nephritis (LN) and chronic glomerulonephritis (GN). The effect of azathioprine on lymphocyte populations was dose dependent; high doses decreased the number of T- and particularly, B-cells, while smaller doses produced a selective depletion of B-cells. The changes in T- and B-cells during prednisolone treatment were variable with alternating increases and decreases in their numbers. The patients with increased B-lymphocyte levels showed the best response to immunosuppressive therapy.

The effects produced by immunodepressants upon the T- and B-lymphocyte systems are important because of the different effector mechanisms of humoral and cellular immunity in the pathogenesis of certain autoimmune diseases. The anti-proliferative effect of cyclophosphamide is known to be more pronounced on B-lymphocytes. With azathioprine the findings appear to be conflicting.

The therapeutic efficacy of corticosteroids and cytostatics is generally associated with inhibition of immunological reactions (in addition to nonspecific anti-inflammatory action), thus leading to their use in patients with high immunological activity. The correlation between the level of T-lymphocytes and disease activity in systemic lupus erythematosus (SLE) is well documented [Schelnberg and Cathcart 1974, Hamilton and Winfield 1979], while the data concerning B-lymphocytes is conflicting [Messner et al. 1973, Arimori et al. 1975, Sandhofer et al. 1975]. The same applies to T- and B-cell numbers in patients with glomerulonephritis [Tishkov et al. 1976, Zucchelli et al. 1976]. Thus further studies of the T- and B-cell levels in SLE and GN patients are warrented.

The present study was designed to: 1) reveal correlations between numbers of T- and B-cells and disease activity in lupus nephritis (LN) and chronic GN; 2) study the effect of long-term therapy with azathioprine and prednisolone on T- and B-cells in LN and GN patients; 3) evaluate the dependence of the efficacy of treatment on the initial T- and B-cell levels.

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Materials and methods

Patients: The levels of T- and B-lymphocytes were studied in 110 patients (70 with GN and 40 with LN) aged 15 to 57 years and in 33 age- and sex-matched normal subjects. The effect of azathioprine and prednisolone on T- and B-lymphocytes was studied in 52 LN and GN patients.

Fifty-eight patients had chronic GN and 12 patients had acute poststreptococcal GN. Renal biopsy specimens were obtained in 37 patients with chronic GN: 11 had mesangio-proliferative GN, 5-mesangio-membranous, 6-membranous GN, 2-mesangio-capillary GN, 2-lobular GN and 11-fibroplastic GN. Immunofluorescence was studied in 28 cases: IgG was demonstrated in glomeruli in 18 cases, IgM – in 6, IgA – in 3 and fibrin – in 4 cases.

At the time of study, 15 of the 40 LN patients had active SLE with nephritis and multiple systemic signs, 13 had active LN without extrarenal manifestations and 12 had inactive disease. Renal biopsy (21 patients) revealed diffuse proliferative LN in 6 patients, focal proliferative – in 8, membranous – in 2 and fibroplastic – in 5. IgG was found in glomeruli in 12 out of 16 cases studied by immunofluorescent methods.

At the start of the study 103 out of 110 patients were receiving no immunodepressive drugs; 7 patients with active SLE were receiving low doses of prednisolone (5–15 mg/day).

The effect of azathioprine was studied in 12 patients (2 with LN and 10 with GN), whereas that of prednisolone was studied in 28 patients (18 with LN and 10 with GN); a combination of azathioprine and prednisolone was studied in 12 patients (2 with LN and 10 with GN). During the first month of treatment investigations were carried out every 7 days and from the second month of treatment every 3–4 weeks.

In order to exclude the possibility of spontaneous variations in T- and B-cell level, studies were repeated (2 to 6 times) for 2 to 64 weeks in 6 healthy donors and in 15 LN and GN patients who were not given any immunosuppressive agents.

Lymphocytes were isolated from heparinized venous blood using a Ficoll-Hypaque gradient. The resulting suspension contained 85–90% lymphocytes with viability greater than 95% as assessed by trypan blue exclusion. Monocytes were detected by incubating mononuclear cells with latex particles.

B-lymphocytes were counted after immunofluorescent labelling of membrane-bound immunoglobulin. The cells were incubated at 37° for 30 minutes before the addition of fluorescent antiserum to eliminate serum IgG fixed to Fc receptors and antilymphocyte antibodies. This allowed the exclusion of cells having receptors for Fc fragmentes of IgG [Lobo et al. 1975] so that only B-lymphocytes were counted. Under these conditions the mean percentage of Ig-bearing B-lymphocytes in normal subjects was 9.7 ± 0.4%.

T-lymphocytes were studied by the E-rosette formation technique using sheep erythrocytes (SRBC) [Jondal et al. 1972], without pretreatment of SRBC with neuraminidase and without the addition of serum to lymphocyte and erythrocyte suspensions. Lymphocytes which did not carry membrane-bound immunoglobulins and which did not form E-rosettes were designated as null cells [Froland et al. 1974]. The percentage of E-rosette forming cells (51.4 ± 2.3%) was lower than that usually described, and the percentage of O-cells was higher and included a small number of T-cells.

Results

The numbers of T- and B-lymphocytes in LN and GN patients are presented in Table 1. During exacerbation of disease the proportion of B-lymphocytes in all groups of patients increased with simultaneous reduction of the proportion of T-cells. These changes were most marked in patients with active SLE (B–19.7 ± 2.0%; T–29.3 ± 3.1%) who also had an increased percentage of null lymphocytes (51.0 ± 3.4%).

Absolute numbers of T- and B-lymphocytes also reflected the activity of disease, but contrary to the percentage counts, differed in GN and LN. Most GN patients had a lymphocytosis with an increased absolute number of B- and null lymphocytes, and a normal T-cell count. On the contrary, in patients with active

Table 1 Levels of B-. T-, O-cells and total lymphocyte count in GN and LN patients before treatment (mean ± SD).

Patients		Lymphocytes						
		Total number	B %	mm³	T %	mm³	O %	mm³
Acute GN	(n=12)	2343±352	12.9±1.8	256±28	39.8±4.5	840±102	47.3±5.4	1284±218
		P<0.02*	<0,02	<0.01	<0.05		>0.05	<0.01
Chronic GN:								
active	(n = 39)	2144±154	16.5±1.1	356±32	42.8±2.8	865±108	41.6±2.6	984±82
		P<0.05	<0.01	<0.01	<0.05			<0.01
inactive	(n=19)	1704±154	9.2±0.9	153±17	48.0±3,1	824±96	44.043.2	779±97
				>0.1				>0.1
LN:								
with systemic								
lesions	(n = 15)	505±44	19.7±2.0	93±10	29.3±3.1	156±26	51.0±3.4	263±35
		P<0.01	<0.01	<0.01	<0.01	<0.01	<0.05	<0.01
isolated	(n=13)	1569±177	17.1±2.4	250±30	35,3±3,2	582±77	48.8±3.9	782±83
		P>0.1	<0.01	<0.01	<0.01	<0.02	>0.05	>0.1
in remission	(n=12)	1430±90	9.6±2.9	140±17	44.3±4.0	621±78	46.1±4.1	672±76
		P<0.01	>0.1	<0.1	>0.1	<0,05	>0.1	
Normals	(n=33)	1764±70	9.7±0.4	173±11	51.4±2.3	844±60	41.6±2.4	682±17

* P values are for comparison with normals.

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