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Azathioprine in Ulcerative Colitis: Final Report on Controlled Therapeutic Trial

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Summary

Eighty patients, all of whom were suffering from a frank clinical attack of ulcerative colitis, were admitted to the trial. The attack was treated with a standard course of corticosteroids and the patients were immediately placed on treatment with either azathioprine in a dose of 2·5 mg/kg body weight or dummy tablets. The trial tablets were continued for one year while the patients were maintained under regular clinical, sigmoidoscopic, histological, haematological, and biochemical surveillance. If a patient relapsed during such maintenance treatment he or she was treated with a further course of corticosteroids without interrupting maintenance treatment.

In the treatment of an actual attack of ulcerative colitis the results in the attacks which brought the 80 patients into the trial show that no benefit came from the addition of azathioprine to a standard course of corticosteroid therapy.

Patients admitted in their first attack of ulcerative colitis showed no benefit from the one-year maintenance treatment with azathioprine, the benefits of which were confined to patients admitted in a relapse of established disease. Even in these the difference between the treated group and the control group failed to reach statistical significance, but the difference was big enough to suggest that there is a prima facie case for regarding azathioprine as of some benefit in this group of patients.

Introduction

In an interim report we dealt with the results obtained in 40 patients with ulcerative colitis treated in a controlled therapeutic trial of azathioprine for one year (Jewell and Truelove, 1972). We admitted a further 40 patients to the trial and report here the clinical results for the whole group of 80 patients.

Patients

All the patients had classical ulcerative colitis. The diagnosis was made on the basis of a history of bloody diarrhoea coupled with sigmoidoscopic evidence of diffuse inflammation, biopsy evidence of an inflammatory reaction compatible with ulcerative colitis, and changes of ulcerative colitis on the barium enema film.

All patients had a frank attack of the disease on admission to the trial. Some were in their first attack of the disease, and others were suffering from a relapse of established disease. It was explained to the patients that a new treatment was being tested and they were free to volunteer to be included. The necessity for repeated attendances and serial sigmoidoscopic examinations with biopsy was included in the explanation. Married women of fertile age were advised to avoid conception during the trial.

Experimental Design

A two-by-three stratified design was used. Patients were treated initially as either inpatients or outpatients depending on an overall clinical assessment of the severity of their attack. They were also subdivided according to the length of history into three categories: first attack; short history (less than five years); and long history (more than five years). As a result of this double specification patients fell into six groups.

Within each of these groups patients were allotted at random to real or dummy azathioprine treatment, a system of restricted randomization being used so that each block of six patients contained three on azathioprine and three on dummy tablets. The trial treatment was prescribed as "azathioprine special," and the hospital pharmacists worked from a master sheet indicating whether a particular patient was to be given real or dummy azathioprine.

The attack which brought the patient into the trial was treated with a standard course of corticosteroids together with general medical measures in the case of the inpatients. The regimen of corticosteroid treatment for outpatients was oral prednisolone 5 mg four times a day and prednisolone disodium retention enemata nightly. If the therapeutic response was good this regimen was maintained for one month and then tailed-off over the next two weeks.

As the attack was severe in all inpatients treatment began with a five-day intensive course of intravenous therapy as follows: nothing by mouth except water, intravenous control of water and electrolyte balance, prednisolone 21-phosphate 40 mg daily in the intravenous fluid, tetracycline 1 g daily in divided doses in the intravenous fluid, and rectal drip of hydrocortisone hemisuccinate sodium 100 mg twice daily. If the clinical response was good this was followed by resumption of feeding and oral prednisolone 40 mg daily in divided doses. When discharged the patients were on the outpatient regimen and treatment was tailed-off after one month from the start of treatment.

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The dose of azathioprine was about 2·5 mg/kg body weight. With the first 40 patients the dose was reduced after three months to 1·5-2·0 mg/kg body weight whereas with the second 40 patients the dose was maintained at 2·5 mg/kg body weight throughout the entire trial period. The dummy tablets were prescribed in an equivalent manner.

The patients were seen at a special clinic at least once a month. At each attendance the symptoms were recorded, a full blood examination was made, and sigmoidoscopy with biopsy was performed. Apart from the first few patients to be admitted all the patients had biochemical observations on the blood at each monthly attendance, using a Technicon 12.

The attack of ulcerative colitis which brought the patient into the trial was classified as mild, moderate, or severe by the criteria of Truelove and Witts (1955). The sigmoidoscopic appearances at each examination were graded from 0 to 3 (0=normal appearances, 1=mild inflammation, 2=moderate inflammation, and 3=severe inflammation). All the biopsy specimens were examined by one pathologist, who classified them according to the criteria of Truelove and Richards (1956) into the following categories: (*a*) no significant inflammation, (*b*) mild to moderate inflammation, and (*c*) severe inflammation.

During the one-year trial period some patients suffered from one or more relapses of the ulcerative colitis. A relapse was defined as the occurrence of diarrhoea with blood in the motions and with sigmoidoscopic evidence of inflammation. Each relapse was treated according to the regimens already outlined. If a patient suffered three relapses during the trial period he was taken out of the trial and treated openly.

A few patients were defined as failures. These were patients who failed to go into clinical remission within six weeks of corticosteroid treatment, either during the attack which brought them into the trial or in a subsequent relapse during the trial period.

TABLE I—*Clinical Severity of Attacks on Entry to Trial and at End of One Month in Two Treatment Groups*

Severity of Attack	On Entry to Trial		After One Month	
	Azathioprine Group	Control Group	Azathioprine Group	Control Group
Remission ..			31	27
Mild	16	17	4	6
Moderate ..	21	19	2	3
Severe ..	3	4	1	2
Failed ..			2	2
Total ..	40	40	40	40

TABLE II—*Sigmoidoscopic Grades on Entry to Trial and at End of One Month in Two Treatment Groups*

Sigmoidoscopic Grade	On Entry to Trial		After One Month	
	Azathioprine Group	Control Group	Azathioprine Group	Control Group
0			15	9
1	7	15	20	18
2	29	21	3	9
3	4	4		2
Failed			2	2
Total	40	40	40	40

TABLE III—*Histological Grades of Rectal Biopsy Specimens on Entry to Trial and at End of One Month in Two Treatment Groups*

Histological Grade	On Entry to Trial		After One Month	
	Azathioprine Group	Control Group	Azathioprine Group	Control Group
1	1	1	24	15
2	20	21	7	9
3	19	18	7	14
Failed			2	2
Total	40	40	40	40

Results

VALUE OF AZATHIOPRINE IN ACUTE ATTACK

As the patients admitted to the trial were all in a frank attack of ulcerative colitis and as they were immediately placed on treatment with azathioprine or dummy tablets as well as a standard regimen of corticosteroid treatment the value of azathioprine in the treatment of an actual attack of the disease could be assessed.

On entry to the trial the azathioprine group and the control group were closely similar with respect to the severity of the attack which brought them into the trial (table I). At the end of one month there was no obvious difference between the two groups. Though the azathioprine group had 31 patients in remission as against 27 in the control group, this difference was so small that it could be expected to occur often by chance. In each treatment group there were two patients who had already failed by the end of one month.

The sigmoidoscopic gradings were roughly similar in the treated and control group at entry to the trial, with the azathioprine group showing the more severe picture. After one month, however, the azathioprine group showed on average a more favourable sigmoidoscopic response though the difference between the two treatment groups was not statistically significant (table II). Likewise, the rectal biopsy findings were closely similar in the two treatment groups on entry to the trial (table III), but after one month the azathioprine group showed a more favourable response to treatment than the control group though the difference was not statistically significant (excluding the two patients in each group who had already failed and had been withdrawn from the trial before the end of the first month), P=0·11.

Hence azathioprine in a dose of 2·5 mg/kg body weight is of negligible value in the treatment of an attack of ulcerative colitis when added to a standard course of corticosteroid therapy.

VALUE OF AZATHIOPRINE AS MAINTENANCE TREATMENT

The clinical responses of the treated and control groups are shown in table IV. The patients on azathioprine had a more favourable course than those on dummy tablets. Thus, there were 16 of the azathioprine-treated patients who were symptom free throughout the trial (after recovering from the original attack) compared with nine of the patients on dummy treatment. At the other extreme only three azathioprine-treated patients were classified as "failures" compared with seven in the dummy-treated group. For statistical analysis the patients in both treatment groups were classified according to two regroupings of the numbers of relapses as follows: (*a*) 0, 1-3, or failure; and (*b*) 0, 1 or 2, or 3 or failure. On Fisher's exact test the significance of the differences between the azathioprine and control groups on both (*a*) and (*b*) regroupings was P=0·18. Thus, the differences between the two treatment groups were not significant at the conventional level of 0·05 probability.

Treatment with azathioprine had no discernible effect on the course of the disease in patients who were admitted to the trial in their first attack of ulcerative colitis (table V). Such differences as existed between the two treatment groups were confined to those patients who were admitted to the trial during a relapse of established disease. Even though the results were still not statistically significant at the conventional level of 0·05 probability, they were close to this value and there is therefore a prima facie case for regarding azathioprine as of some value in the maintenance treatment of ulcerative colitis which has become chronic. Further analysis of the data has shown that this beneficial effect of azathioprine on established ulcerative colitis was manifest during the first six months of the trial period and continued to show itself during the second six months.

The effect of azathioprine as a maintenance treatment was closely similar in the first part of the trial when the dose was reduced to 1·5-2·0 mg/kg body weight after the first three months to that observed in the second part of the trial when the dose was

TABLE IV—*Detailed Clinical Results of Maintenance Therapy over One Year in Two Treatment Groups. Results are Numbers of Patients*

No. of Relapses	Azathioprine Group							Control Group						
	Patients in First Attack		Patients in Relapse				Total	Patients in First Attack		Patients in Relapse				Total
			Short History		Long History					Short History		Long History		
	I.P.	O.P.	I.P.	O.P.	I.P.	O.P.		I.P.	O.P.	I.P.	O.P.	I.P.	O.P.	
0	3	4	1	2		6	16	2	4			2	1	9
1		2		3		2	7	1	3		3		1	8
2	2	1		1		2	6	1	1				3	5
3	2	1		3		2	8	1			4		6	11
No. of failures:	1			1		1	3	2		1	2		2	7
Total	8	8	1	10	0	13	40	7	8	1	9	2	13	40

I.P. = Inpatient. O.P. = Outpatient.

TABLE V—*Clinical Course during Trial in Two Treatment Groups of Patients according to whether Patients entered Trial in First Attack of Ulcerative Colitis or in Relapse*

No. of Relapses	Admitted in First Attack		Admitted in Relapse	
	Azathioprine Group	Control Group	Azathioprine Group	Control Group
0	7	6	9	3
1-2	5	6	8	7
3 or Failed	4	3	7	15
Total	16	15	24	25
Significance of Differences*	N.S.		P = 0·055	

*Fisher's exact test.

maintained at 2·5 mg/kg body weight throughout the whole trial period of one year.

COMPARABILITY OF TREATED AND CONTROL GROUPS

The design of the trial was calculated to produce similar treatment groups and this was borne out. The sex and age distributions were similar (table VI). The two treatment groups contained roughly equal numbers of patients admitted in their first attack of the disease, in a relapse of established disease of short history, and in a relapse of established disease of long history (see table IV). Within each of these categories the numbers of inpatients and outpatients were similar in the two treatment groups, which is an indication that they were about equal as regards the severity of the illness on admission to the trial. This is supported by data on the clinical severity of the attack, the sigmoidoscopic picture, and the histological grading of the rectal biopsy specimen at the time of admission to the trial (see tables I-III).

We may therefore conclude that the treatment and control groups were closely similar in all relevant respects.

TABLE VI—*Sex and Age Distribution in Two Treatment Groups*

	Sex		Age (Years)				
	Male	Female	<30	30–	40–	50–	⩾60
Azathioprine group ..	21	19	7	12	10	6	5
Control group	21	19	8	11	10	6	5

SIDE EFFECTS

The serial haematological observations showed no example of frank bone-marrow depression. Among the first 40 patients two developed isolated low white cell counts of 3,300/mm³ and 3,700/mm³, but when the code was eventually broken it was found that only one of these was on azathioprine tablets. Among the second 40 patients one showed a low white cell count of 2,200/mm³ once, and he was found to have been receiving azathioprine.

One patient developed nausea, abdominal discomfort, and diarrhoea after having been in the trial for four weeks though the ulcerative colitis was in remission. The azathioprine special was stopped and there was rapid relief from the symptoms. Resumption of the azathioprine special was followed by a recurrence of the same symptoms and once again with relief when the azathioprine special tablets were stopped. When the code was broken he proved to have been on real azathioprine. The blood count remained normal throughout these episodes and the results of liver function tests were also normal.

Two patients complained of excessive loss of head hair during the trial period but both proved to have been treated with dummy tablets. One patient developed a generalized erythematous rash which cleared when the trial tablets were stopped and recurred when they were restarted. When the code was broken she was found to have been on azathioprine.

In effect, the complications of azathioprine during this trial were few and not dangerous.

IMMUNOLOGICAL OBSERVATIONS

During the second half of the trial immunological studies were made on the effect of azathioprine on subpopulations of circulating lymphocytes. In addition, quantitative studies of the immunocytes of the lamina propria of the rectal biopsy specimens were made by a pathologist. These observations indicated that the patients on azathioprine had greatly reduced production of plasma cells and K cells, similar to the effects seen in patients previously studied (Campbell *et al.*, 1974). The full results will be published separately.

Discussion

This controlled therapeutic trial enabled us to draw some firm conclusions about the value of azathioprine in the treatment of ulcerative colitis.

When attacks of ulcerative colitis are being treated with corticosteroids the addition of azathioprine confers no benefit. When used as a maintenance treatment azathioprine has no influence on the course of the disease during the year after a first attack. Among patients who present with a relapse of established disease, however, maintenance treatment with azathioprine reduces the relapse rate. Though our results just failed to achieve statistical significance we think there is a prima facie case for regarding them as showing a genuine effect of azathioprine therapy on the course of the disease even though it is obvious that azathioprine does not represent a major advance in therapy.

Most attacks of ulcerative colitis can be checked by corticosteroid therapy combined with appropriate general medical measures. The prevention of recurrences remains a major prob-

lem of medical management. Maintenance treatment with moderate doses of corticosteroids is completely ineffective as well as carrying the risks of long-term corticosteroid administration (Truelove and Witts, 1959; Lennard-Jones *et al.*, 1965). By contrast, sulphasalazine has emerged as an effective agent for maintenance treatment. Though it is not universally successful it nevertheless reduces the recurrence rate to about a quarter of that experienced by control groups, and this suppressive effect is sustained during maintenance treatment for at least five years (Misiewicz *et al.*, 1965; Dissanayake and Truelove, 1973). Our results show that azathioprine does not exert such a powerful suppressive action as sulphasalazine, which remains the most important medical agent for maintenance treatment.

If azathioprine has any place in the medical treatment of ulcerative colitis it is as maintenance treatment in patients who have failed to do well on conventional treatment with corticosteroids and sulphasalazine and in whom there is some good reason for not performing or deferring proctocolectomy. If azathioprine is used close supervision is necessary because of the risk of bone-marrow suppression and hepatic toxicity. Possibly also azathioprine predisposes to subsequent neoplasia though decisive evidence is not yet available outside the field of organ transplantation (*British Medical Journal*, 1973).

We thank Dr. A. H. Griffith of the Wellcome Foundation for his co-operation, including the supply of trial tablets. Dr. R. Whitehead classified the biopsy specimens, Drs. A. C. Campbell and I. C. M. MacLennan made the immunological investigations, and Dr. J. M. Skinner made quantitative studies on immunocytes in biopsy specimens.

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Longitudinal Study of Untreated Chemical Diabetes

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Summary

More information is needed about the "natural history" of early diabetes mellitus. A report is presented of the progress over one to nine years of 72 patients who formed the control group of a clinical trial of chlorpropamide and placebo in the management of subclinical diabetes. Most patients showed no deterioration of carbohydrate tolerance, and only four (5·6%) progressed to overt diabetes. The findings of other published series are reviewed. Studies of the effect of treatment of early diabetes must be large scale and long term, and an untreated control group must be included to prevent apparent improvement in carbohydrate tolerance being wrongly attributed to the effect of therapy.

Introduction

Surprisingly little is known about the natural history of untreated subclinical diabetes mellitus. It is widely assumed that progression to overt diabetes will occur, and while it is known that such deterioration may be rapid or very slow (Marble, 1971) information is lacking on several aspects of early diabetes. An uncontrolled clinical trial of the long-term effect of chlorpropamide in subclinical diabetes (Stowers and Helgason, 1965; Stowers, 1973) has shown improvement of carbohydrate tolerance to normal in some groups of patients, especially those below the age of 35 years. Possibly this is due to the β-cytotrophic effect of the sulphonylureas which has been clearly shown in animals (Loubatières *et al.*, 1956). Results of the uncontrolled trial emphasized the obvious need for a long-term trial to include an untreated control group. A double-blind, controlled, clinical trial to compare the effect of chlorpropamide and placebo in subclinical diabetes was therefore established in 1963 under the auspices of the British Diabetic Association (B.D.A.). We report here on the progress of the placebo-treated control group of chemical diabetics (see B.D.A. classification of diabetes, Fitz-Gerald and Keen, 1964).

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Method

Patients who had given their informed consent were admitted to the trial if, on testing with an intravenous glucose tolerance test (I.V.G.T.T.), they were shown to have chemical, asymptomatic diabetes—that is, a normal fasting blood sugar level but an abnormal curve thereafter. The original screening was made because of asymptomatic glycosuria, a strong family history of diabetes, "temporary" diabetes within the previous 10 years, or reproductive performance resulting in a baby over 4,500 g at birth, a stillborn infant with islet cell hyperplasia of pancreas not due to rhesus incompatibility, 10 or more chidren, two or more "unexplained" stillbirths, or excessive weight gain during pregnancy. Since the trial was designed in 1963 we have refined the selection criteria—for example, by defining a significantly overweight baby as one above the 95th percentile weight for gestation and maternal weight (Thomson *et al.*, 1968). For admission to this part of the trial the body weight of all patients had to be within the 75th percentile for age, sex, and height (after Kemsley, 1951-2). Allocation to the active drug or placebo group was randomized. Patients were reviewed at least twice yearly and had an annual I.V.G.T.T., stopping tablets for three weeks before the test to obviate any immediate pharmacological effect on the I.V.G.T.T. in those patients on the active drug. Blood sugar estimations were done on capillary specimens by the AutoAnalyzer ferricyanide method (Hoffman, 1937).

A.W.L. broke the randomization code and studied the 72 placebo-treated patients (38 women, 34 men) who had been in the trial for at least one year (mean 4·2 years). Their ages at the time of entry ranged from 19-54 years (mean 39·7 years).