Controlled therapeutic trial of levamisole and sulphasalazine in acute ulcerative colitis

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SUMMARY Forty five patients with acute ulcerative colitis were randomly allocated to receive (a) sulphasalazine, (b) levamisole, or (c) a combination of sulphasalazine and levamisole. Each group contained 15 patients. The ulcerative colitis activity index (UCAI), the remission and relapse rates were compared at three monthly intervals for one year. The UCAI fell in each group. Detailed analysis of all clinical and biochemical parameters used for estimation of UCAI showed that the only difference was in patients receiving combined therapy who continued to have a raised ESR and platelet count. Fewer patients, however, went into remission on levamisole therapy (46.6%) compared with the other two groups (66.6%). The cumulative relapse rate was 20% for those receiving levamisole compared with 6.6% in the other groups. Side effects were observed in 20% of patients receiving levamisole, 26% receiving sulphasalazine, and 40% in those having combined therapy. The results indicate that levamisole is unlikely to have a major role in the management of patients with ulcerative colitis.

Ulcerative colitis is an inflammatory disease of the colonic mucosa. Its aetiopathogenesis is poorly understood although aberrations in the immune system may be involved, both humoral^{1,2} and cellular³⁻⁷ responses being implicated.

As levamisole is able to modulate the humoral and cellular immune responses^{8,9} thereby acting as an immunostimulant, it was proposed to assess its therapeutic benefit in patients with ulcerative colitis. Immunosuppressive agents, apart from corticosteroids,¹⁰ have proved disappointing in the management of acute disease; antimetabolites, alkylating agents, and antilymphocyte globulin have been tested.¹¹⁻¹⁴ It seemed reasonable, therefore, to test an immunostimulant and the present trial has investigated the efficacy of levamisole used alone or in combination with sulphasalazine in patients with active ulcerative colitis. Treatment was continued for one year.

Methods

PATIENTS

Forty five patients in an acute attack of ulcerative colitis were entered into the trial. The purpose and

the design of the trial was explained before obtaining the patient's consent. The details of the patients are shown in Table 1. The diagnosis of ulcerative colitis was made on commonly accepted criteria – that is, the present and past symptoms (bloody diarrhoea, fever, loss of weight, etc), sigmoidoscopic appearances, histological examination of a rectal biopsy specimen, and the appearance of a barium enema. All cases were referred to the International Programme for Inflammatory Bowel Disease organised by the Research Committee of OMGE and proved to meet 99.9% of their diagnostic criteria. The ulcerative colitis activity index (UCAI) was defined according to our modification of the Talstad and Gjone criteria¹⁵ (Table 2). Patients with a score of 6–15 were considered as having mild ulcerative colitis, a score of greater than 15 represented severe disease, while a score of 5 or less was regarded as remission. On entry into the trial, patients were randomly allocated to one of the three groups: (a) sulphasalazine, 6 g daily until remission occurred, followed by 3–4 g daily as maintenance therapy, (b) levamisole 150 mg orally twice a week for the first two weeks and then once a week thereafter, (c) levamisole plus sulphasalazine in the doses used in groups (a) and (b). Allocation was performed using a table of random numbers.

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Table 1 Details of patients

	Sulphasalazine	Levamisole	Sulphasalazine and levamisole
Number	15	15	15
Age in years	36.0 /20-66/	40.3 /22-73/	43.7 /20-74/
Male/female	9/6	8/7	7/8
Duration of the disease in years	5.4 /0.4-13.0/	5.2 /0.2-18.0/	6.3 /0-15.0/
Number of previous attacks	1-2 3-9 10	7 4 2	7 7 1
Mean symptom free period before last attack in months	5.4 /0-16/	9.1 /0-24/	8.2 /0-20/
Disease extent: rectal	2	4	3
left side colon	11	11	10
total colon	2	—	2
Treatment in previous 6 months			
sulphasalazine	12	12	12
rectal steroids	—	—	1
oral steroids	1	—	1

Each patient was given a diary card on which to record the daily number of stools, the presence or absence of blood, the degree of abdominal pain, temperature and body weight. The UCAI was measured on the first visit and every three months during the year of treatment. At each visit, sigmoid-

oscopy was performed with biopsy and blood samples were obtained for a full blood count and ESR, serum iron, total protein, and albumin concentration. A barium enema was performed before entry into the trial and at the end of the one year treatment period. Supportive therapy in the form of vitamins and iron was prescribed as required.

Table 2 Disease activity in ulcerative colitis. Modification of Talstad and Gjone classification¹⁵

Disease activity parameters		Ulcerative colitis maximum score
Diarrhoea	3-5 motions/day 1 6-10 motions/day 2 >10 motions/day 3	3
Fever	38-39°C >39°C	2 2
Tachycardia	>100/min	2
Abdominal pain		1
Weight loss	5-10 kg >10 kg	1 2
Radiograph of colon	slight moderate severe toxic	1 2 3 4
Proctoscopy	slight severe	1 2
ESR	10-30 mm/h >30 mm/h	1 2
Hb	10-11.8 g/100 ml <10 g/100 ml	1 2
Leucocytes	>1 × 10 ⁹ /ul	2
Thrombocytes	>4 × 10 ⁵ /ul	2
Total protein	5.6-6.5 g/100 ml <5.5 g/100 ml	1 2
Albumin	2.6-3.3 g/100 ml <2.5 g/100 ml	1 2
Serum iron	51-70 ug/100 ml <50 ug/100 ml	1 2
Sum maximum score		30

STATISTICS

Results were analysed using the χ^2 test and Student's *t* test for paired and unpaired data. Significance was taken as $p < 0.05$.

Results

COMPARABILITY OF GROUPS

Patients in each group were comparable in age and sex distribution, duration of the disease, number of previous attacks, extent of disease and treatment during the six months before entering the trial.

ULCERATIVE COLITIS ACTIVITY INDEX (UCAI)

Figure 1 shows the UCAI for each group on entry into the trial and at each three month period during the subsequent year. At each time interval there were no significant differences between the groups. For all patients there was a fall in the UCAI during treatment between the groups. For all patients there was a fall in the UCAI during treatment regardless of which therapeutic regimen they were receiving.

Figure 2a shows that the daily number of stools each patient passed progressively diminished during treatment and there was a small rise in body weight during the trial period. No differences were seen between groups. Figure 2b shows the laboratory

Fig. 1 Effect of sulphasalazine, levamisole and sulphasalazine plus levamisole on ulcerative colitis activity index (UCAI) score. Mean results and SD are indicated.

data. After six and 12 months of therapy, the ESR and platelet count was significantly higher in group (c) compared with group (a). All other clinical and biochemical parameters did not differ among the groups.

The sigmoidoscopic appearances are shown in Table 3.

REMISSION AND RELAPSE RATES

For groups (a) and (c), 10 patients (66.6%) in each group went into remission on treatment compared with seven patients (46.6%) in the levamisole treated group (group b). This difference was not significant. In group (b), three patients (20%) relapsed compared with only one patient (6.6%) in each other group. This difference was not significant.

SIDE EFFECTS

Side effects were observed in six patients from group (c) (Table 4). In groups (a) and (b), side-effects were observed in three and four patients respectively. Two patients in group (b) and two in

group (c) had such severe side effects (headache, leucopenia, skin rash) that treatment had to be stopped.

Discussion

The efficacy of levamisole in a variety of inflammatory disorders is well documented.¹⁶⁻²⁰ The drug may also be useful in the management of Crohn's disease.²¹⁻²³ In ulcerative colitis, levamisole was not effective in a group of seven patients but clinical details of these patients was poorly documented.²¹

The present study has compared levamisole with sulphasalazine in patients with active ulcerative colitis. Although the UCAI was reduced in all three treatment groups, fewer patients went into remission – that is, UCAI 5 – on levamisole compared with those receiving sulphasalazine. The subsequent relapse rate was higher in the levamisole treated group than in those receiving sulphasalazine. Those differences, however, were not significant. The combination of sulphasalazine and levamisole had no benefit over sulphasalazine alone.

Table 3 Proctoscopic findings during ulcerative colitis therapy

	<i>Sulphasalazine and levamisole</i>									<i>Levamisole</i>
Duration of treatment (months)	0	6	12	0	6	12	0	6	12	
Patients (no.)	15	14	14	15	15	12	15	14	10	
Ulcers	15	8	1	15	4	3	15	6	2	
Friability (bleeding to touch only)	15	11	8	15	7	3	15	11	3	
Spontaneous bleeding	15	10	7	15	8	2	15	10	2	

Table 4 Number of side effects. 1—during 0–6 months, 2—6–12 months, 3—withdrawal of the drugs caused by the side effects

	Sulphasalazine			Sulphasalazine and levamisole			Levamisole		
	1	2	3	1	2	3	1	2	3
Indigestion	1	1	—	—	—	—	1	—	—
Headache	—	—	—	—	1	1	1	1	1
Leukopenia	—	—	—	—	1	1	—	—	—
Skin rash	1	—	—	1	1	—	—	1	1
Mouth ulcers	—	—	—	—	1	—	—	—	—
Oedema cruris	—	—	—	—	1	—	—	—	—
Total	2	1	—	1	5	2	2	2	2

Fig. 2 Effect of sulphasalazine (—), levamisole (---) and sulphasalazine used together with levamisole (-.-.-) on clinical (a) and on biochemical (b) indices of disease activity. * $p < 0.05$

The comparatively low dose of levamisole used in this trial has been shown to be associated with few side effects although its immunostimulatory properties are maintained.²⁴ Twenty six per cent of patients receiving levamisole, however, developed side effects which is similar to that reported in other series using a higher dosage.⁸ Thus no reduction of side effects was seen using the lower dose. In

conclusion, the results of this trial suggest that levamisole is of little benefit in the management of ulcerative colitis. They may also suggest that the pathogenesis of the disease is not a result of an impaired immune response.

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