

## Levamisole in rheumatoid arthritis

### Final report on a randomised double-blind study comparing a single weekly dose of levamisole with placebo

#### MULTICENTRE STUDY GROUP\*

**SUMMARY** The therapeutic effect of a single weekly dose of levamisole in patients with rheumatoid arthritis was compared with placebo for 6 months in a 13-centre double-blind controlled study. 281 patients with classic or definite rheumatoid arthritis and active disease were evaluated. A single weekly dose of 150 mg levamisole was superior to placebo in controlling disease activity. A single weekly dose of 50 mg levamisole had an intermediate effect. Adverse reactions occurred in approximately 40% of the patients with 150 mg levamisole and in approximately 20% of the patients with 50 mg levamisole or placebo. In comparison with the classical dosage schedule of levamisole (150 mg on 3 consecutive days each week) a single weekly dose of 150 mg levamisole was found to be slightly less effective but much better tolerated.

The therapeutic effect of levamisole in patients with rheumatoid arthritis has been established in several controlled studies.<sup>1,2</sup> At the usual therapeutic dose of 150 mg levamisole on 3 or 7 consecutive days each week, however, severe adverse reactions are frequent. Preliminary data from a small multicentre trial showed that treatment with 150 mg levamisole once weekly was effective but caused significantly fewer side effects.<sup>2</sup> The present study is an extension of this trial, the data of which are included in the present analysis.

#### Materials and Methods

**Investigators.** Thirteen study centres in 7 countries participated in this double-blind placebo-controlled study. Each centre was asked to enter 2 or 3 study groups with at least 12 patients in each.

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**Co-ordinators.**—Dr E. Scharenberg (Argentina), Dr J. Adams (Great Britain), Mr G. Eisen (USA), Mr H. Scheijgrond, and Dr J. Symoens (central co-ordination).

**Patients.** Outpatients were admitted with definite or classic rheumatoid arthritis by the American Rheumatism Association criteria,<sup>3</sup> that is, a history of rheumatoid arthritis for at least 6 months and active disease<sup>4</sup> that was not controlled by, or that progressed despite, the optimum use of anti-inflammatory drugs. Patients who were unreliable, under 16 years of age, pregnant, or had been treated with basic antirheumatics such as gold, D-penicillamine, antimalarials, immunosuppressives, or levamisole within the 3 months before the start of the trial were excluded.

**Experimental drugs.** Tablets containing 50 or 150 mg levamisole or identically formulated placebo tablets were randomly allocated within each study centre for 2 or 3 treatment groups of 12 patients each. Placebo or 50 or 150 mg levamisole was given once weekly at night. The drugs and placebo were specially packaged to ensure that the study was double-blind.

**Concomitant treatments.** Patients continued to take the anti-inflammatory or analgesic drugs which they were already taking on admission to the trial. Phenylbutazone and its analogues were prohibited. Doses of concomitant drugs could be increased or decreased during the trial but not during the month before admission to the study. Doses of corticosteroids were limited to the equivalent of 10 mg prednisolone daily. No new anti-inflammatory, analgesic, or antirheumatic therapy was started from 1 month before the start of the trial until its end.

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*Clinical and biological assessments.* Patients were evaluated by the same investigator at the start, at mid study, and at the end of the 6-month study. Mandatory assessments were Ritchie index,<sup>5</sup> the number of tender and of swollen joints, pain measured by Huskisson's visual analogue method,<sup>6</sup> duration of morning stiffness, erythrocyte sedimentation rate (ESR) by the Westergren method, and rheumatoid factor titre measured by the latex or Rose-Waaler tests. At each visit the patient was asked about adverse reactions without the investigator suggesting that these should be expected.

*Data analysis.* All data were recorded on standard record forms and sent to the co-ordination centre for analysis. Nonparametric tests were used for statistical analysis. Changes between the start and 3 or 6 months within treatment groups (intragroup changes) were evaluated by the Wilcoxon matched-pairs signed-ranks test,<sup>7</sup> and differences in changes between groups (intergroup) were evaluated by the Mann-Whitney U test,<sup>7</sup> each with 2-tailed probabilities. To reduce distortion, patients who were withdrawn because of pronounced deterioration were included in the analysis with a no-change value for each measure.

Individual response to treatment was evaluated by means of a mathematical model designed by Lewi and Symoens<sup>8</sup> to express by one score the degree of change in 6 measures of disease activity: Ritchie index, number of tender and of swollen joints, pain, morning stiffness, and ESR. A negative total score indicates deterioration, a positive score up to 130 indicates stabilisation of the disease or moderate improvement, and a total score above 130 indicates marked improvement. Statistical analysis of the total response to treatment was by the chi-square test.

## Results

### PATIENTS

Two hundred and eighty-one patients entered the study, 60 in the control group, 81 in the group on 50 mg levamisole once weekly, and 140 in the group on 150 mg levamisole once weekly. Fifty (83%) patients of the control group, 67 (83%) patients of the 50 mg levamisole group, and 111 (79%) patients of the 150 mg levamisole group completed the 6-month trial. Deterioration caused 4 withdrawals in the control group, 3 withdrawals in the 50 mg levamisole group, and 4 withdrawals in the 150 mg levamisole group. Other early withdrawals were mainly due to lack of co-operation of the patients in all study groups and to adverse reactions in the 150 mg levamisole group (Table 1).

Table 1 *Number of patients studied*

	Control	Levamisole		Total group
		50 mg	150 mg	
Start	60	81	140	281
3 months				
Evaluable	57	70	127	254
Withdrawn, inefficacy	1	2	0	3
Withdrawn, adverse reactions	0	4	9	13
Withdrawn, unrelated reason	2	5	4	11
6 months				
Evaluable	50	67	111	228
Withdrawn, inefficacy	4	3	4	11
Withdrawn, adverse reactions	1	4	16	21
Withdrawn, unrelated reason	5	7	9	21

Sex distribution, mean age, body weight, duration of disease, previous basic treatment, anatomical stage, functional class, and the various measures of disease activity at the start of the study were similar in all 3 study groups except for the number of tender joints and for the amount of pain, which were slightly but statistically significantly higher in the 50 mg levamisole group (Table 2).

### EFFICACY

*Clinical and biological assessment.* Fig. 1 shows the median changes in the various mandatory measures of disease activity at 6 months. Changes are expressed as a percentage of the median prestudy values. After 3 months of treatment the patients treated with 150 mg levamisole once weekly had improved more than the patients of the other 2 groups, as determined by the number of swollen joints, morning stiffness, and ESR. At 6 months this difference was marked for each measure of disease activity, and statistically significant improvement over placebo was seen for number of swollen joints, pain, and morning stiffness.

*Rheumatoid factor.* At 6 months the latex titre had decreased in one-third of the patients receiving either dose of levamisole and in 13% of the patients receiving placebo ( $p < 0.05$ , signed-rank test, 2-tailed).

*Withdrawal because of ineffective treatment.* Patients could be withdrawn because therapy was ineffective only when exacerbation necessitated more active therapy. Four (7%) patients in the control group, 3 (4%) in the 50 mg levamisole group, and 4 (3%) in the 150 mg levamisole group were withdrawn for this reason.

*Degree of responsiveness (total score).* At 6 months 16 patients (30%) in the control group, 14 (20%) in the 50 mg levamisole group, and 19 (17%) in the

Table 2 Patient and disease characteristics at start

	Control		Levamisole			
			50 mg		150 mg	
	n	Value*	n	Value*	n	Value*
Females	60	78	78	74	139	78
Age (years)	60	51 (27-72)	77	52 (21-76)	137	53 (22-77)
Weight (kg)	60	64 (37-113)	74	61 (44-96)	133	64 (39-110)
Duration of disease (years)	59	8.0 (0.3-37)	80	6.0 (0.5-26)	134	7.5 (0.5-29)
Previous basic antirheumatics	60	48	81	58	140	55
Anatomical stage 1/2/3/4	57	2/68/28/2	73	16/38/36/10	134	6/54/37/3
Function class 1/2/3/4	60	8/72/20/0	81	12/54/32/1	140	8/62/30/0
Ritchie index (0-78)	60	22.0 (8-68)	81	20.0 (5-65)	140	18.5 (1-60)
Tender joints (number, 0-26)	60	12.0 (6-26)	81	13.0 (2-26)	140	11.0 (1-25)
Swollen joints (number, 0-23)	60	10.0 (0-18)	81	7.0 (0-19)	140	8.0 (0-18)
Pain (1-100 mm)	59	54.0 (0-100)	81	67.0 (10-100)	140	60.0 (2-100)
Morning stiffness (min)	60	60.0 (0-1440)	80	60.0 (0-360)	140	60.0 (0-1440)
Erythrocyte sed. rate (mm/1 h)	60	41.5 (10-150)	81	38.0 (3-125)	140	39.5 (4-129)
Latex, % positive	45	51	69	65	116	56
Latex titre**		3 (0-6)		4 (0-10)		3.5 (0-9)
Rose-Waaler, % positive	15	73	46	70	48	63
Rose-Waaler titre***		7 (2-8)		7 (0-10)		6 (2-11)

\* Median (and range) or percentage of patients.

\*\* Numbers 1, 2, 3, etc. correspond to titres 1/20, 1/40, 1/80, etc.

\*\*\* Number 1, 2, 3, etc. correspond to titres 1/2, 1/4, 1/8, 1/16, etc.

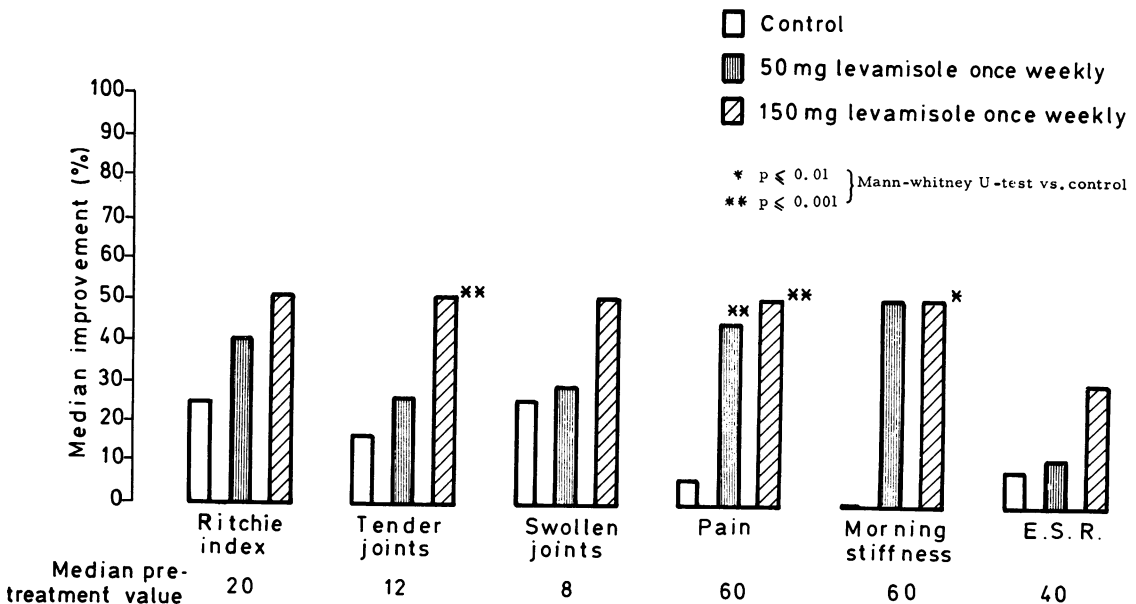


Fig. 1 Changes of disease activity (medians) during 6 months of treatment with 50 or 150 mg levamisole or placebo (paired data).

150 mg levamisole group had deteriorated (total score <0), or were withdrawn for inefficacy; 5 patients (9%) in the control group, 12 (17%) in the 50 mg levamisole group, and 27 (23%) in the 150 mg levamisole group had markedly improved (global

score >130) (Fig. 2). Statistical analysis of the overall response to treatment demonstrates superiority of 150 mg 3 to 7 days weekly over 150 mg once weekly ( $p=0.0076$ ) and superiority of 150 mg once weekly over placebo ( $p=0.0012$ ).

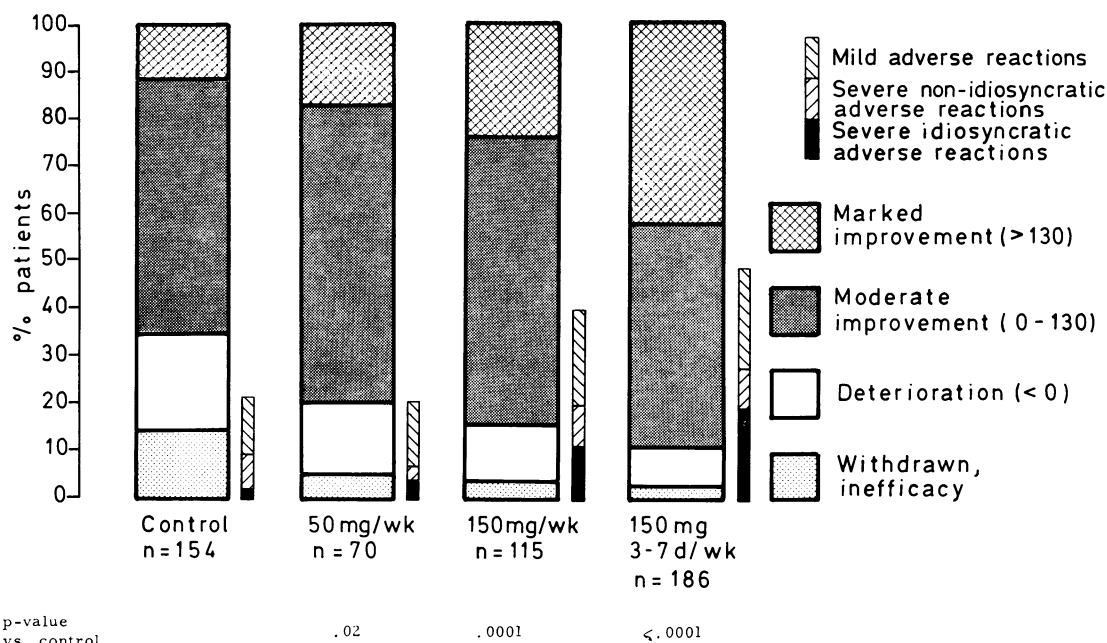


Fig. 2 Comparison of 6-month total score distribution and of the incidence and severity of side effects of patients who participated in the Eular study (levamisole 150 mg 3-7 days/week) and in the present study (levamisole 50 and 150 mg/week). The control patients of both studies have been pooled. Statistical comparison with control was by means of the Mann-Whitney U test.

#### ADVERSE REACTIONS

The adverse reactions reported in each treatment group are summarised in Table 3.

**Withdrawal for adverse reactions.** Twenty-three patients, mainly in the 150 mg levamisole group, were withdrawn for gastrointestinal complaints, influenza-like illness, skin rash, or agranulocytosis. Influenza-like illness was not accompanied by agranulocytosis or leucopenia. 70% of the with-

drawals because of side effects occurred during the first 3 months of the study.

**Frequency and severity of adverse reactions** Approximately 40% of the patients who received 150 mg levamisole and 20% of the patients who received 50 mg levamisole or placebo had adverse reactions during the 6-month trial period. Each adverse reaction was reported on a special form and graded for severity. A reaction was regarded as being severe when it incapacitated the patient in his usual activities, or when it constituted a definite hazard to the patient. Mild and severe nonidiosyncratic reactions occurred in 17, 18, and 30% of the patients in the control, 50 mg levamisole, and 150 mg levamisole groups respectively. Severe, idiosyncratic adverse reactions (agranulocytosis, severe rash, severe febrile or influenza-like illness, and severe mouth ulceration) occurred in 11% of the 150 mg levamisole-treated patients, in 4% of the 50 mg levamisole-treated patients, and in 3% of the controls. The 2 control patients with severe idiosyncratic adverse reactions had a rash which necessitated a temporary arrest of treatment.

Table 3 Type of adverse reactions and, in parentheses, withdrawal because of side effects (number of patients)

	Levamisole		
	Control (n=60)	50 mg (n=81)	150 mg (n=140)
Gastrointestinal	10 (1)	8 (2)	34 (8)
Skin rash	5	2	9 (2)
Agranulocytosis	0	1 (1)	1 (1)
Leucopenia	0	0	2
Leucocytosis	0	0	1
Influenza-like illness	0	11 (1)	28 (5)
Mouth ulcers	0	1	1
Fever	0	2	6
Neurological	1	1	10*
Sicca syndrome	0	1	0
Proteinuria	0	0	1
Increased weight	0	0	1

\*Dysgeusia (2 patients), hyperosmia (7), insomnia (1).

**Other withdrawals.** In the control group 5 patients were unco-operative or failed to return. In the 50 mg

levamisole group 6 patients were unco-operative or failed to return, and 1 patient was admitted to hospital elsewhere because of severe bronchitis. In the 150 mg levamisole group 7 patients were unco-operative or failed to return, 1 patient became pregnant during the first month of treatment, and 1 patient was admitted to hospital for gastric ulceration.

#### DISCUSSION

The design and methods of this study are essentially the same as those of a previous multicentre study performed under the auspices of the European League against Rheumatism (Eular), in which 2 dose regimens of levamisole (150 mg on 3 or 7 consecutive days each week) were compared with placebo in 363 patients.<sup>1</sup> Six centres which participated in the Eular study also participated in the present study. For these reasons, and because the patients of the Eular trial and of the present trial were comparable at the start with regard to patient and disease characteristics, the results of both trials may be compared.

Fig. 2 shows the overall responsiveness and the incidence of adverse reactions after 6 months of treatment with each dose regimen used in both studies. The responses of both control populations being comparable, the results have been pooled. The response to levamisole improves with increasing doses and frequency of administration, but likewise the incidence of severe idiosyncratic reactions increases. Skin rash, the most frequent severe side effect in the Eular study, was rare when levamisole was given once weekly; conversely, influenza-like illness and gastrointestinal intolerance were more frequent with the weekly 150 mg dose, the latter probably because the weekly dose was a single intake. The incidence of agranulocytosis decreased from 2% in the Eular study to 0.9% in the present study.

Reduction of the frequency of treatment with levamisole from 3 days to 1 day per week thus slightly reduces the efficacy but also reduces the incidence of severe side effects. Further reduction of the dose to 50 mg once weekly gives marginal efficacy and virtual absence of severe side effects. A single weekly dose of 150 mg levamisole is therefore the regimen of choice during the first months of treatment, when most side effects occur. Moreover, early detection of imminent agranulocytosis is possible by weekly white blood cell monitoring.<sup>9</sup> After 6 months the frequency of treatment can be increased to 2 or 3 nonconsecutive days per week, depending on the response.

#### References

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