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A clinical trial of glycosaminoglycan-peptide complex ('Rumalon') in patients with osteoarthritis of the knee**G. Katona, M.D.***Department of Rheumatology,
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Summary

A clinical trial was undertaken in 50 patients with osteoarthritis of the knee to assess the therapeutic value of glycosaminoglycan-peptide complex in treatment. The first year consisted of a randomized, double-blind, placebo-controlled, parallel-group trial (25 patients in each group), after which all patients received active treatment for a further 2 years. Treatment consisted of three 8-week courses in the first year and 2 such courses per year in subsequent years, each consisting of 2 ml intramuscular injections given 3 times per week. Patients were permitted to continue taking anti-inflammatory drugs and to receive physiotherapy during the trial period. At the end of the first year of the trial (double-blind phase), there were no significant differences between the two treatment groups. However, after the second year, those patients who had received glycosaminoglycan-peptide complex for 2 years had significantly greater improvements in night pain and rest pain than did those who had received active treatment for only 1 year. At the end of 3 years (when half the patients had received active treatment for 2 years and half for 3 years), there were significant overall improvements in relation to rest pain, pain on walking and morning stiffness, but not in respect to night pain, pain on standing or climbing stairs. At the same time, improvements were seen in radiological severity of disease (assessed double-blind) in 16% of patients, with 'no change' in 74% and deterioration in 10%, these figures being considerably better than might be expected with conventional therapy. Glycosaminoglycan-peptide complex was extremely well tolerated.

Key words: Glycosaminoglycan-peptide complex — osteoarthritis

Introduction

Osteoarthritis or degenerative joint disease is the most common rheumatic complaint and has considerable socio-economic consequences. Published epidemiological studies^{12,15,16,28,29} vary in their estimates of the incidence of osteoarthritis in particular joints, probably due to differences in methods of assessment and diagnosis. Whereas Wagenhäuser²⁸ found the knee to be the most commonly affected joint, especially over the age of 40 years, Kettelkamp and Colyer¹⁵ found it to be the third most affected joint, after osteoarthritis of the spine and hip.

There are marked ethnic variations in the incidence of osteoarthritis. The Pima Indians and Blackfoot Indians are among the most frequently affected (74% of

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women and 56% to 61% of men over the age of 30 years), whilst the incidence of osteoarthritis of the knee is lowest (18%) in the Eskimos on the east coast of Greenland.¹ Similarly, there are variations in site and clinical features of osteoarthritis and also differences between the sexes as regards incidence of the disease.²¹ Forman *et al.*¹⁰ studied 682 subjects over the age of 60 years and found a significantly greater incidence of knee arthrosis in men than in women, with a larger number of advanced cases among black women. Conversely, Wagenhäuser²⁸ found no sex differences in incidence of the disease.

In general, the incidence of osteoarthritis increases with age,^{21,26} but there are uncertainties as to whether this remains true right across the age spectrum for knee arthrosis. Bland⁶ found an incidence of 35% in 30-year olds and of greater than 85% in 70 to 79-year olds, confirming findings of a Swiss study²⁸ that the incidence was 1.5% in the 20 to 24-year group, rising to 100% in those over 70 years of age. Conversely, other studies¹⁰ have found an essentially consistant morbidity (of 50%) and severity of disease throughout the age range 60 to 99 years.

It is now generally agreed⁷ that the earliest pathological changes of osteoarthritis occur in the articular cartilage. Biomechanical and/or biochemical factors lead to a disturbance of cartilage metabolism (proteoglycan loss) associated with damage to chondrocytes and resulting increases in the activity of catabolic enzymes.⁷ In contrast with conventional types of therapy (analgesics, anti-inflammatory agents), which seek only to provide symptomatic relief, the object of chondroprotective therapy is to facilitate regeneration of cartilage, with normalization of its structure and metabolism.²⁵ Several large clinical studies and studies in experimental animals have demonstrated the beneficial effects of one of these agents, glycosaminoglycan-peptide complex ('Rumalon'†), on the process of degenerative disease.^{2,4,11,18,19,23}

The present study was undertaken because of the epidemiological importance of osteoarthritis of the knee and to evaluate the 'chondroprotective' activity of glycosaminoglycan-peptide complex.

Patients and methods

The study comprised two phases over a total period of 3 years. The first year consisted of a randomized, double-blind, placebo-controlled parallel-group trial. During the second and third years, all patients received active therapy. Fifty ambulant patients with clinically and radiologically diagnosed knee arthrosis (Stage II or III, according to the Kellgren and Lawrence¹⁴ classification) were included in the trial.

After selection for the trial and giving their consent, patients underwent baseline assessments and then commenced on trial medication. During the first year, patients were randomized to receive in a double-blind manner either glycosaminoglycan-peptide complex (Group A) or placebo (Group B). Treatment during this first year consisted of 3 courses of treatment, each of 8-weeks' duration and separated by approximately 3 months without trial medication. Each course of treatment consisted of 2 ml intramuscular injections 3-times per week. In the second and third years, all patients received two 8-week treatment courses per year, separated

†trade mark, Robapharm

by intervals of approximately 16 weeks, each course consisting of 3 intramuscular injections of 2 ml glycosaminoglycan-peptide complex per week. Throughout the trial, patients were permitted to continue receiving anti-inflammatory drugs and physiotherapy, as required.

Assessments were undertaken at trial entry and at 4-weekly intervals thereafter. Pain at rest, pain at night, pain on walking, pain on standing and climbing stairs were all graded by patients on a 5-point scale (0=none, 1=slight, 2=moderate, 3=severe, or 4=very severe/disabling). Duration of morning stiffness was also evaluated. The ranges of both active and passive movement of the knees were assessed with a goniometer. Laboratory screening investigations (haematology, blood chemistry, urine) were undertaken at trial entry and at 6-monthly intervals during the trial. Radiographs of the knees were obtained at trial entry and at yearly intervals thereafter; these were assessed double-blind by a rheumatologist and a radiologist, according to the Kellgren and Lawrence classification.¹⁴ Patients were questioned regarding any possible side-effects at each assessment visit.

Appropriate statistical significance tests (Student's t-test, Wilcoxon's test, Mann-Whitney test, etc.) were used to examine the significance of changes within and between the groups. The threshold for significance was taken as $p=0.05$.

Results

Fifty patients entered the trial, 25 being allocated to each treatment (glycosaminoglycan-peptide complex and placebo) for the first year of the trial. Their mean age was 61.9 years (range 46 to 77 years), their mean weight 63.4 kg (range 49 to 79.5 kg), and their mean duration of known disease 5.1 years (range 1 to 13 years). The groups were well matched with respect to these features, with no significant differences between the groups (Table I).

Table I. Details of patients studied: number of patients

Patients	Glycosaminoglycan-peptide complex (Group A)	Placebo (Group B)
No. studied	25	25
Sex: Male	1	2
Female	24	23
Age (years): Mean	61	62.7
Range	49 to 77	46 to 76
Weight (kg): Mean	62.6	64.2
Range	49 to 79.5	51 to 76
Duration of disease (years):		
Mean	5.6	4.5
Range	1 to 13	1 to 10

At the end of the first year (double-blind phase), significant improvements were seen in virtually all indices of pain (night pain, pain on standing, climbing stairs, walking) in the glycosaminoglycan-peptide complex-treated patients (Table II). In the placebo-treated group, significant improvements were seen in relation to

Table II. Assessment of pain severity on entry and after treatment in the two groups: number (%) of patients

Assessment	Group A			Group B		
	Week 0 (n=25)	Week 48 (n=21)	Week 96 (n=18)	Week 0 (n=25)	Week 48 (n=23)	Week 96 (n=18)
<i>Resting pain</i>						
Absent	13 (52)	16 (76.2)	18 (100)	11 (44)	14 (60.8)	15 (83.3)
Mild	2 (8)	3 (14.3)		6 (24)	6 (26.1)	2 (11.1)
Moderate	9 (36)	2 (9.5)		6 (24)	3 (13.1)	
Severe						
Very severe	1 (4)					
Significance	↔ N.S. ↔	↔ p<0.05 ↔		↔ N.S. ↔	↔ N.S. ↔	
		↔	p<0.05		↔	
<i>Night pain</i>						
Absent	11 (44)	13 (61.9)	17 (94.4)	11 (44)	13 (56.5)	13 (72.2)
Mild	2 (8)	6 (28.6)	1 (5.6)	5 (20)	8 (34.8)	4 (22.2)
Moderate	11 (44)	2 (9.5)		7 (28)	2 (8.7)	
Severe	1 (4)			2 (8)		1 (5.6)
Very severe						
Significance	↔ p<0.01 ↔	↔ p<0.05 ↔		↔ N.S. ↔	↔ N.S. ↔	
		↔	p<0.05		↔	
			↔	p<0.02	↔	
<i>Pain on standing</i>						
Absent	5 (20)	13 (61.9)	17 (94.4)	4 (16)	7 (30.4)	6 (33.3)
Mild	4 (16)	6 (28.6)	1 (5.6)	12 (48)	13 (56.5)	6 (33.3)
Moderate	14 (56)	2 (9.5)		6 (24)		4 (22.2)
Severe	2 (8)			3 (12)	3 (13.1)	2 (11.2)
Very severe						
Significance	↔ p<0.01 ↔	↔ N.S. ↔		↔ N.S. ↔	↔ N.S. ↔	
<i>Pain on climbing stairs</i>						
Absent		5 (23.8)	4 (22.2)	3 (12)	3 (13.1)	3 (16.7)
Mild	3 (12)	10 (47.6)	3 (16.7)	2 (8)	11 (47.8)	2 (11.1)
Moderate	12 (48)	2 (9.5)	6 (33.3)	2 (8)	6 (26.1)	6 (33.3)
Severe	10 (40)	4 (19.1)	2 (11.1)	10 (40)	3 (13.0)	7 (38.9)
Very severe		3 (16.7)				
Significance	↔ p<0.005 ↔	↔ N.S. ↔		↔ p<0.005 ↔	↔ N.S. ↔	
<i>Pain on walking</i>						
Absent	2 (8)	9 (42.8)	7 (38.9)	1 (4)	8 (36.4)	5 (27.8)
Mild	2 (8)	6 (28.6)	5 (27.8)	5 (20)	7 (31.8)	2 (11.1)
Moderate	16 (64)	5 (23.8)	3 (16.7)	13 (52)	4 (18.2)	9 (50.0)
Severe	5 (20)		1 (5.6)	6 (24)	2 (9.1)	2 (11.1)
Very severe		1 (4.8)	2 (11.0)		1 (4.5)	
Significance	↔ p<0.05 ↔	↔ p<0.05 ↔		↔ p<0.01 ↔	↔ N.S. ↔	

N.S.=not significant

pain on climbing stairs and pain on walking (Table II). The differences between the groups were not statistically significant (Table II), partially because of the relatively small numbers of patients and the other concomitant therapy received by both groups.

At this time, significant improvements were seen in glycosaminoglycan-peptide complex-treated patients with respect to a number of the indices of joint movement (Table III), i.e. active flexion (bilateral), angle of flexion (bilateral) and angle of extension (right side only). In the placebo-treated group, significant improvements were seen in relation to active flexion (bilateral), passive flexion (bilateral) and in the angle of flexion (right side only). Again, there were no significant differences between the two groups.

Table III. Measurement of the angle of movement in the knee joints before and after treatment in the two groups: mean values

Measurement (degrees)	Group A			Group B		
	Week 0 (n=25)	Week 48 (n=21)	Week 96 (n=18)	Week 0 (n=25)	Week 48 (n=23)	Week 96 (n=18)
<i>Active flexion</i>						
Right	41.6	45.6*	46.2*	41.2	47.6*	48.2*
Left	40.0	46.8*	45.2*	41.3	47.9*	46.9*
<i>Passive flexion</i>						
Right	50.0	53.6	54.0†	49.4	54.1*	58.5*
Left	48.2	54.9	50.8	48.9	55.6*	53.1
<i>Range of flexion</i>						
Right	138.6	132.7*	135.7	137.4	131.5*	131.5*
Left	140.4	131.4*	138.1	136.8	131.9	134.1
<i>Range of extension</i>						
Right	179.0	178.3*	178.6	178.6	178.9	178.6
Left	178.4	178.5	180.0	178.0	179.6	179.2

*p<0.05, compared with Week 0, †p<0.05, between-groups difference

At the end of the second year (Table II), those patients who had received glycosaminoglycan-peptide complex for 2 years (Group A, having been randomized to receive active medication in the first year), showed significant improvements in respect to pain at rest, pain at night, and pain on walking. In contrast, those who had received active medication for only 1 year (Group B, having received placebo in the first year) showed no significant improvement in respect to pain (Table II). Significant differences between the two groups were seen in relation to pain at rest and pain at night (Table II), both of which are clinically very important indices. At this time, active flexion (bilateral), passive flexion (right side only) and angle of flexion (right side only) were significantly increased in the group who had initially received placebo (Group B), whereas only active flexion (bilateral) increased significantly in Group A, i.e. those who had received glycosaminoglycan-peptide complex throughout the 2 years (Table III); the differences between the groups were significant (in favour of the initially placebo-treated group) only in relation to passive flexion (right side only).

Morning stiffness decreased significantly during the first year in glycosaminoglycan-peptide complex-treated patients, and this effect was maintained at the end of the second year (Table IV). In those patients who received placebo during the first year (Group B), there was no significant change during that year, but there was a significant improvement during the following year of active treatment (Table IV).

Table IV. Duration of morning stiffness before and after treatment in the two groups: mean values

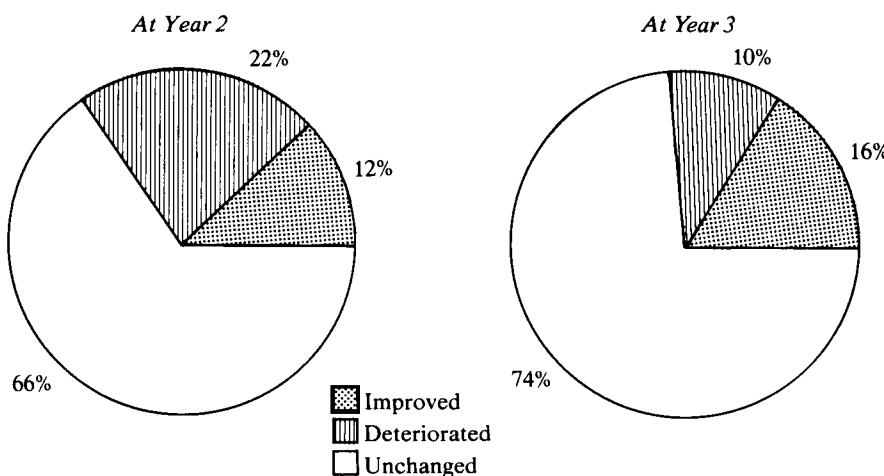
Assessment	Group A			Group B		
	Week 0 (n=25)	Week 48 (n=21)	Week 96 (n=18)	Week 0 (n=25)	Week 48 (n=23)	Week 96 (n=18)
Duration (min)	10.6	2.4	0	8.8	4.5	0
Change from Week 0		-8.2	-10.6		-4.3	-8.8
Significance		p<0.05	p<0.05		N.S.	p<0.05

N.S.=not significant

Over the full 3-year period, significant overall improvements (in all patients) were seen in respect of pain at rest, pain on walking and morning stiffness, but not in relation to pain at night, pain on standing or climbing stairs.

Double-blind assessment of radiographs was made, using the method of Kellgren and Lawrence,¹⁴ at the end of the second year (representing 2-years' active therapy for the glycosaminoglycan-peptide complex group and 1-year's active therapy for the placebo group). There was improvement in 12% of the total patient group, deterioration in 22% and 'no change' in 66%. At the end of the third year (representing 3-years' and 2-years' active therapy, respectively), further improvement

Figure 1. Assessment of radiological findings: percentage of all patients



was seen, namely improvement in 16%, deterioration in 10% and 'no change' in 74% (Figure 1).

Glycosaminoglycan-peptide complex was well tolerated. Three patients experienced adverse experiences (headache, nausea, and dizziness) of moderate intensity which, however, did not lead to a discontinuation of therapy. There were no serious adverse effects and, in particular, no allergic phenomena were observed. Laboratory investigations revealed no values outside the normal ranges.

Eighteen patients (7 in Group A, 11 in Group B) were withdrawn from the trial prematurely (Table V). In none of these cases was withdrawal occasioned by adverse effects and in only 3 cases (1 in Group A, 2 in Group B) was lack of therapeutic efficacy the reason.

Table V. Status of patients at the end of the 3-year trial period: number of patients

Patients	Group A	Group B	Total
No. entered	25	25	50
No. still being treated after 3 years	18	14	32
<i>Reason for drop-out</i>			
'Cure'	3	2	5
Inadequate treatment	1	2	3
Journey time too long		1	1
No reason given	3	4	7
Other diseases		2	2

Discussion

During the first year of the trial (double-blind phase) there were only small and non-significant differences in favour of glycosaminoglycan-peptide complex as compared with placebo; this was probably due to the relatively small number of patients and to the confounding effects of concomitant treatment with non-steroidal anti-inflammatory drugs and physiotherapy.

At the end of the second year of the trial, improvements in pain at rest and at night were significantly greater in those who had received active treatment for 2 years (Group A) than in those who had received glycosaminoglycan-peptide complex for only 1 year (Group B). These improvements continued into the third year of the trial. These findings are noteworthy because of the particular importance of these symptoms to patients. In patients who received placebo during the first year (Group B), significant improvements were not seen until 2 years after the change to active therapy at the end of the first year.

Although the possibility of spontaneous clinical regression of osteoarthritis can no longer be ruled out completely,^{6,17,22} this remains a rare occurrence. Osteoarthritis, therefore, can still be regarded as an essentially progressive disease, even though its course in individual patients is unpredictable.¹⁵ It has been estimated that spontaneous improvement of osteoarthritis occurs in 6% to 8%, whilst progression is seen in 25% to 30%.^{3,27} The course of the disease seems less favourable in patients treated with indomethacin.²⁴ The prognosis of osteoarthritis of the

knee is generally regarded as being worse than that of osteoarthritis of the hip,^{5,13,20} particularly when degenerative changes involve the inner tibio-femoral joint space.²⁶ Radiological progression of disease has been reported in 42% of 48 patients with degenerative genu varum.^{11,15}

In the present study, the observed progression rates of 22% in the second year and 10% in the third year are considerably lower than the norms defined by the various published studies. Even more remarkable are the unexpectedly high regression rates of 12% in the second year and 16% in the third year. Despite the absence of any controls during the second and third years, treatment with glycosaminoglycan-peptide complex would seem to be the only explanation for the observed objective (radiological) changes. These findings confirm the previous results from both uncontrolled trials⁸ and long-term controlled trials.^{9,23}

Glycosaminoglycan-peptide complex proved to be exceptionally well tolerated, which contrasts with the relatively high level of adverse reactions associated with most anti-arthritic drugs, and suggests that this agent may be particularly suitable for long-term therapy in patients with degenerative joint disease.

In conclusion, and having regard to other recently published work,^{9,23} the results of this trial appear to confirm that glycosaminoglycan-peptide complex is efficacious in the treatment of osteoarthritis of the knee. In contrast with existing steroid and non-steroid anti-inflammatory drugs, it appears to inhibit progression of the disease as well as giving symptomatic relief, and is also associated with far fewer side-effects. These findings suggest that glycosaminoglycan-peptide complex may be a valuable agent for the long-term treatment of patients with knee arthritis.

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