Osteoarthritis and Cartilage (2000) **8,** 335–342
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doi:10.1053/joca.1999.0307, available online at http://www.idealibrary.com on IDEAL®
1063–4584/00/050335+08 $35.00/0

Osteoarthritis and Cartilage
Journal of the OsteoArthritis Research Society International

A 5-year randomized controlled, double-blind study of glycosaminoglycan polysulphuric acid complex (Rumalon®) as a structure modifying therapy in osteoarthritis of the hip and knee

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Summary

Objective: To determine the structure (disease) modifying effect of a glycosaminoglycan polypeptide association complex (GP-C; Rumalon®) in patients with knee and hip osteoarthritis (OA).

Methods: Double-blind, randomized, placebo-controlled five-year study. Primary assessment criterion was change in radiographic joint space width between baseline and follow-up at 5 years. Secondary outcome criteria included Lequesne algofunctional index (LAI), pain on passive motion and consumption of non-steroidal antiinflammatory drugs (NSAIDs). The patients received 10 courses of injections of placebo or GP-C 2 ml intramuscularly in 5 years (two courses each year). Each course included 15 injections administered twice weekly.

Results: There were 277 patients with knee OA and 117 patients with hip OA. Control and GP-C treated groups were comparable as to sex, age, duration of disease, body weight, X-ray stage and value of LAI at the baseline. Knee joint space at 5 years decreased 0.37±0.08 (mean±standard deviation) mm for GP-C and 0.42±0.08 mm for placebo groups (P=0.68). Hip joint space at 5 years decreased 0.21±0.08 mm for GP-C and 0.22±0.08 mm for placebo groups (P=0.53). In a subset of patients with hip OA, Kellgren–Lawrence≥2 and JSW≥1 mm, there was a trend in favor of GPC for lower joint space narrowing in 5 years (P=0.11). In addition, there were no statistical differences between the treatment groups in LAI, pain on passive motion and consumption of NSAIDs. Side-effects after GP-C (14.5%) were rare, mild and not more frequent than in the placebo group (15%).

Conclusion: We were not able to demonstrate a structure modifying effect of GP-C in OA of the hip or knee. Radiographic progression of OA in both knee and hip OA was lower than expected in both study groups. © 2000 OsteoArthritis Research Society International

Key words: Osteoarthritis, X-ray progression, Rumalon®, Disease modification, Knee, Hip.

Introduction

Osteoarthritis (OA) is the most common joint disorder. In population studies, radiographic signs appear in most people above 65 years of age, and in the population above 75 years, radiographic OA is 80%.[1]

Present day therapy of OA combines non-pharmacologic and pharmacologic programs aimed at symptom relief.[2] Although there are no medications yet proven to alter the course of OA, there is considerable current research directed at structure (disease) modification. These agents are intended to prevent, retard or reverse the morphological changes of the cartilage in OA in the studies in humans.[3] These drugs may or may not have an independent effect on symptoms.[4]

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Support of grant IGA MZ CR No.2153-3, Robapharm and Pierre Fabre Pharmaceuticals.

Rumalon® (Robapharm; Pierre Fabre) is a glycosaminoglycan peptide complex (GP-C). It is an extract made of young bovine cartilage and bone marrow, produced by a standardized method. One millilitre of GP-C contains 2.5 mg of glycosaminoglycan complex (GAG) of molecular weight over 100 000 Daltons. The GAG consists of chondroitin-4-sulfate (64.5%), chondroitin-6-sulphate (16.5%), chondroitin (9.5%), dermatan-sulfate (3.4%), hyaluronate (2.1%) and keratan-sulfate (4.0%).

GP-C has been suggested as a disease modifying agent by *in vitro*, *in vivo* and in human studies.

In vitro studies by Bollet[5] found increased incorporation of isotope labeled sulfur into chondrocytes after adding GP-C to the chondrocyte cell culture. Additional studies by Adam,[6] demonstrated increased incorporation of ^{3}H labeled proline into collagen after the administration of GP-C *in vitro*. Also, GP-C has shown inhibition of hyaluronidase, papain and collagenase activity *in vitro*.[7] GP-C prevented the catabolic effects of interleukin-1 on chondrocytes.[8]

The disease modifying potential of GP-C was tested in a rabbit model of OA after medial menisectomy.[9] In animals

treated with GP-C, the extent of cartilage abrasion was lower by gross examination and histologic score. There were lower levels of neutral metalloproteinases and higher levels of tissue inhibitor of proteinase (TIMP) in the GP-C treated than the placebo-treated animals. It was concluded that prophylactic therapy with GP-C effectively in reduced the severity of OA in this animal model.

In human studies, 50 patients with knee OA were treated for 3 years with either ibuprofen or ibuprofen plus two series of GP-C per year.[10] After 2 years of treatment, the GP-C treated patients reported less night and resting pain, less pain during walking, shorter periods of morning stiffness and required less analgesia.

Clinical studies of Rejholec examined GP-C vs placebo in knee OA (5 years) and hip OA (up to 16 years).[11] Radiographic progression was less in the GP-C patients. For secondary outcomes, the GP-C group had fewer inflammatory exacerbations, mobility of the signal joint was better, and there was an improved ability to climb up and down stairs. Joint replacement surgery was performed in six of the GP-C group and 17 of the controls.

Additional study seemed appropriate as several of the clinical trials have been questioned on the basis of methodological issues. The objective of the present study was to examine the disease modifying effects of long-term therapy with GP-C in patients with OA of the hip or knee.

Methods

PATIENTS

Consecutive patients seen in the Prague Institute of Rheumatology with pain in at least one knee and/or hip were screened for OA by ACR classification criteria that include the radiograph.[12,13] The age of patients was limited to between 40 and 70 years. Additional inclusion criteria for the knee were patients with knee pain plus radiological evidence of joint space narrowing (JSN) in at least one of the three knee compartments and/or osteophytes and/or subchondral sclerosis. Additonal inclusion criteria for the hip were patients with hip pain plus radiological evidence of JSN in one of the two views and/or osteophytes and/or subchondral osteosclerosis.

Criteria for exclusion were the following: those with knee pain due to other causes were to be excluded; generalized OA (OA in three or more joint areas); severe or 'end-stage' OA (JSW<1 mm with severe disability preventing the patient from attending the outpatient department); presence of primary inflammatory joint disease; surgery on knees and hips in the past; coexistent severe disease of kidneys or liver; administration of steroids for any reason in the prior 3 months and long-term administration of slow-acting drugs for OA for the preceding 3 months (e.g., intraarticular hyaluronate, oral glucosamine-sulfate, oral chondroitin-sulfate).

PROCEDURE

This was a double-blind, controlled, parallel group, randomized five-year study involving three clinical centers with all laboratory examinations and all X-ray images performed at the Prague Institute of Rheumatology.

Consecutive patients were block randomized into two groups, with a block size of six. Both GP-C and placebo were prepared in identical vials. The products were identical in color, smell and consistency and were labeled with the randomization code. The placebo contained the diluent (saline) used in the preparation of the GP-C. Patients received 15 (twice weekly) intramuscular injections per course, and two courses of injections per year for 5 years (i.e. a total of 10 courses) of GP-C or placebo. There was no cross-over of therapy.

Table I
Numeric system for estimating the use of analgesic vs anti-inflammatory doses by regular users of several non-steroidal antiinflammatory drugs

NSAID	Analgesic dose	Antiinflammatory dose
Diclofenac	≤75 mg	>75 mg
Ibuprofen	<1600 mg	≥1600 mg
Indomethacin	<75 mg	≥75 mg
Salicylates	<2500 mg	≥2500 mg
Tiaprofenic acid	≤300 mg	>300 mg
Flurbiprofen	≤150 mg	>150 mg
Piroxicam	≤10 mg	≥20 mg
Tolfenamic acid	≤200 mg	>200 mg
Ketoprofen	≤150 mg	>150 mg
Naproxen	≤500 mg	>500 mg
Tolectin	<1200 mg	≥1200 mg
Tramadol	≤100 mg	≥150 mg
Lonazolac ca	<1200 mg	≥1200 mg
Nabumetone	<1000 mg	≥1000 mg

Non-steroidal antiinflammatory drugs (NSAIDs) and analgesics were permitted at the discretion of the investigator. The type and dose of NSAID was recorded as follows: (1) no NSAID was consumed in the prior month; (2) NSAIDs were ingested irregularly (i.e. not every day); (3) analgesic doses of NSAIDs were ingested daily; or (4) antiinflammatory doses of NSAIDs were ingested daily. A numerical system was developed to separate levels 3 and 4 for each of the available NSAIDs (Table I).

During the trial the following were not permitted: intra-articular or systemic corticosteroids; opiate analgesics; slow acting agents for OA (defined above). Physical therapy was permitted and its application monitored.

Patients were examined at baseline and subsequently every 3 months for 5 years. Study medication was provided by the coordinating center at 6 month intervals. A daily log recorded adverse events. Radiographs were obtained yearly (i.e. six images of the signal joint in 5 years).

PRIMARY EFFICACY VARIABLE

The primary outcome measure was change in the radiographic joint space from baseline to final visit at 5 years. The initial 1989 protocol listed six primary outcome variables: clinical state, patient questionnaire, joint space width (JSW), summary score of selected X-ray criteria, need for surgery and consumption of analgesics. During the trial, and prior to any data analysis, the protocol was amended to focus on the single variable above.

SECONDARY EFFICACY VARIABLES

Secondary outcome measures included the Lequesne algofunctional index (LAI) of knee or hip OA,[14] pain on passive motion of the signal joint, global evaluation and consumption of NSAIDs. The LAI is a composite index of

pain and function. The questionnaire was completed by the patient at each visit with the assistance of a trained nurse.

Global evaluation of OA was reported at each visit separately by the patient and the physician using the following 5-point scale to make comparisons with the pre-study condition: −2=much worse, −1=worse, 0=no change, +1=better, +2=much better. Passive motion of the signal joint was performed by the patient and pain recorded on a 4-point scale: 0=none, 1=mild, 2=moderate, 3=severe.

RADIOLOGICAL EVALUATION

All joint imaging was performed at the Prague Arthritis Institute. All radiographs were obtained by one radiological technician using a single X-ray machine (Siemens, Sire Graph C, Erlangen). X-rays were obtained yearly.

For the knee, the X-ray cassette film was placed 1.15 m from the tube. Anterioposterior weight-bearing radiographs were obtained with the patient's heels and toes together and knees fully extended. The X-ray beam was horizontal and the central beam was fluoroscopically directed at the center of the joint space at the level of the tibial tubercle. For subsequent studies, the repositioning of the patient was guided by the original radiograph, and the same radiographic techniques were repeated (i.e. kilovolts, milliamps, milliseconds). No other mechanical guides were used for repositioning.

For the hip, the X-ray cassette film was located 1.15 m from the tube. A single anteroposterior weight bearing pelvic radiograph was obtained with the patient's toes together. The X-ray beam was horizontal and the central beam was directed 5 cm above symphysis pubis (not fluoroscopically placed). As above, for repeat studies the repositioning of the patient was guided by the original radiograph, and the same radiographic techniques (i.e. kilovolts, milliamps, milliseconds) were used. No other mechanical guides were used for repositioning.

MEASURING JOINT SPACE WIDTH

Joint space width (JSW) was measured on the anteroposterior radiograph by the method of Lequesne,[15] using a ×10 magnifying lens marked with a 20 mm scale at 0.1 mm intervals. The site of the tibiofemoral compartment selected for interpretation was based on the site on the baseline radiograph at which the joint space was narrowest. If the JSW was equal in both tibiofemoral compartments, the narrowest point of the compartment adjacent to the largest osteophyte was measured. If the JSW were equal and the osteophytes were equal in size, the medial compartment was measured at its narrowest point. If there was no narrowest point of the compartment, the midpoint of the compartment was measured.[16] A drawing pencil was used to mark the radiograph for the measuring points.

Two readers were trained by a skilled radiologist to read JSW. Readers reviewed radiographs independently. If the two JSW readings were within 0.3 mm, the mean of the two values was recorded as the final reading. If the difference between the two JSW readings was >0.3 mm, the radiographs were reinterpreted by both readers and if the readings were then within 0.3 mm the mean was recorded. If the second reading confirmed a difference of >0.3 mm, the average of the four readings was recorded.

Measurement of JSW and Kellgren–Lawrence grading was performed on the baseline and final radiographs at the same time. Radiographs were blinded as to patient name, date and chronology of the radiograph. Kellgren Lawrence grading was estimated by both readers, guided by a radiographic atlas.

Selection of the signal joint was based on the more painful hip or knee on passive motion. If pain was equal, the signal joint was from the side with the more severe changes on the radiograph. If both symptoms and radiographs were equal, the right side became the signal joint.

INTRAOBSERVER AND INTEROBSERVER ERROR

Intraobserver error for each reader was estimated on 10 randomly chosen X-rays, measured six times, spaced over 10 days. For the knee, the intraclass correlation was 0.99 for reader A (coefficient of variation 2.0%) and 0.98 for reader B (coefficient of variation 3.6%). For the hip, the intraclass correlation was 0.98 for reader A (coefficient of variation 5.5%) and 0.97 for reader B (coefficient of variation 6.2%).

The interobserver error was assessed on all radiographs. For the knee, the interclass correlation was 0.97 (coefficient of variation 6.6%) prior to adjudication and 0.98 (coefficient of variation 5.2%) after adjudication. For the hip, the interclass correlation was 0.99 (coefficient of variation 4.0%) prior to adjudication and 0.99 (coefficient of variation 3.6%) after adjudication.

STATISTICAL EVALUATION

Sample size: based on prior clinical trials, it was estimated that 400 patients would be needed to demonstrate benefit on the six initial variables; i.e. 200 for hip and 200 for knee (programme N of IDV Gauting/Munich).

Data analysis: based on reduction of JSW from baseline to completion of the study at 5 years using analysis of covariance with the last observation carried forward missing value strategy for intent-to-treat analysis. With a single outcome variable, no correction of a type I alpha error (considered equal to 5%) was deemed necessary. Knees and hips were evaluated separately.

The two sided student's *t*-test with nominal value of 5% was selected as the method for comparison for additional analyses. For the adjusted treatment effect, a 95% interval of reliability was established. In addition, a non-parametric analysis of covariance by ranks was calculated.

Additional analyses included those who completed the study (per protocol analysis), yearly changes in JSW, intent-to-treat analysis and completer analysis was performed on those with a JSN of >1 mm at baseline, and those with an initial Kellgren–Lawrence grade ≥ 2.[17]

Results

KNEE: PATIENT POPULATION

There were 280 patients recruited into the study. Adequate data was available in 277 for intent-to-treat analysis because three patients did not have a second radiograph. The 5-year study was completed by 250 patients (90.3%) (Fig. 1). Reasons for premature withdrawal were adverse reaction in 15 (5.4%), loss of follow-up in seven (2.6%), and patient decision in five (1.8%). There were no demographic differences between the GP-C and placebo treatment groups (Table II). The

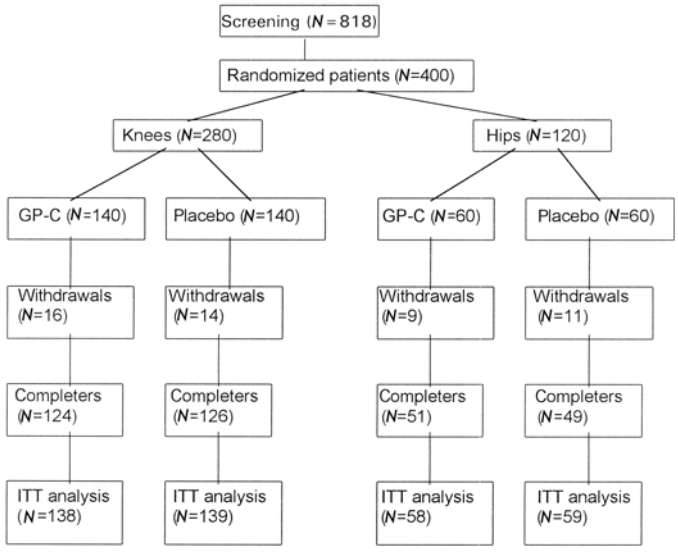

Fig. 1. Flow diagram of the study population.

Table II
Patient population

		Knee		Hip	
		GP-C (*N*=138)	Placebo (*N*=139)	GP-C (*N*=58)	Placebo (*N*=59)
Sex (%)	Men	37 (27)	33 (24)	21 (36)	18 (31)
	Women	101 (73)	106 (76)	37 (64)	41 (70)
Age (years) (mean±S.D.)	Men	59.1±7.4	60.6±8.4	52.6±9.2	57.8±9.4
	Women	59.2±7.2	58.6±7.9	57.4±8.1	55.8±8.9
	All	59.2±9.7	59.1±8.0	55.6±8.7	56.4±9.0
BMI (kg/m^2) (mean±S.D.)	Men	30.4±3.2	31.3±3.6	28.8±4.1	29.3±2.7
	Women	31.1±2.9	31.7±3.6	30.4±2.9	31.4±4.9
	All	30.8±4.2	31.5±3.7	29.9±4.4	30.9±3.1
Duration of disease (months) (mean±S.D.)		73.7±96.1	69.1±59.4	70.7±63.2	87.8±79.7
LAI (Points) (mean±S.D.)		8.9±3.5	9.2±3.4	8.2±3.3	8.5±3.8
Stage Kellgren–Lawrence (%)	0	4 (3)	3 (2)	8 (14)	10 (17)
	1	19 (14)	18 (13)	17 (29)	21 (36)
	2	20 (19)	20 (14)	6 (10)	8 (14)
	3	21 (41)	67 (48)	22 (38)	15 (25)
	4	33 (24)	31 (22)	5 (9)	5 (9)
Joint space width (mm)		4.2±1.7	4.1±1.7	3.6±1.2	3.8±1.3
Pain on passive movement (%)	None	53 (38)	40 (29)	16 (28)	11 (19)
	Moderate	71 (51)	80 (58)	32 (54)	40 (71)
	Severe	14 (10)	19 (14)	10 (18)	6 (10)

study included 72% women, average age 58 years, average BMI 31, average LAI 9, disease duration for 6.2 years, and an average ISK score of 9. The patients had diverse radiographic scores, averaging 2.7 for the knee by Kellgren–Lawrence grading. The mean width of the narrowest point of the radiographic joint space was 4.2 mm for the knee. Pain was mostly moderate.

KNEE: JSN

Results of the primary efficacy variable for the knee are recorded in Table III. There was no difference in the progression of JSN between the GP-C and placebo groups. The actual change in Kellgren–Lawrence grade is recorded in Table IV. There was a trend toward more frequent changes into higher stages with those on placebo (P=0.094).

A subset analysis of those with knee OA completing the study with an initial JSN of ≥1 mm and at least a Kellgren–Lawrence grade of 2 included 86 from the GP-C group and 95 from the placebo group. The JSW was reduced in GP-C group from 4.31±0.14 to 3.81±0.18 mm (change −0.49±0.11 mm) and in placebo group from 4.14±0.14 to 3.64±0.16 mm (change −0.50±0.10 mm) after 5 years (P=0.97) (Table V).

The changes in JSW from knee OA in yearly intervals are demonstrated in Table V. There are no differences in values between the study group in any year. The decrease of JSW was not linear, but was most rapid in the first year (−0.32 mm) with a slower progression from the second to the fifth year. The mean annual rate of JSN was 0.1 mm.

Table III
Change in knee joint space between GP-C and placebo groups

Study group	Baseline (mean±S.E.M.)	End point		Change (mean±S.E.M.)
		Raw means±S.E.M.	Adjusted means±S.E.M.	
GP-C	4.23±0.15	3.86±0.16	3.81±0.08	−0.37±0.08
Placebo	4.13±0.14	3.71±0.15	3.76±0.08	−0.42±0.08
Difference	0.10±0.20		0.05±0.11	0.04±0.11
95% CI	[−0.30; +0.50]		[−0.16; +0.25]	[−0.17; +0.25]
P (1) value	*P*=0.63		*P*=0.66	*P*=0.68
P (2) value	*P*=0.22		*P*=0.69	*P*=0.77

P (1): Difference between GP-C and placebo groups; parametric evaluation (two sided *t*-test).
P (2): Difference betweeen GP-C and placebo groups; non-parametric evaluation (Wilcoxon test).

The number of patients who progressed in the GP-C group ≥ 0.5 mm in the 5 years was 31/88 (36%) in the GP-C group vs 29/95 (31%) in the placebo group.

HIP: PATIENT POPULATION

There were 120 patients recruited with adequate data to analyse 117 by intend-to-treat analysis because three patients did not have a second radiograph.

There were no differences in the demographics between GP-C and placebo treatment groups (Table II). There were 64% women, average age 56 years, average BMI 30, disease duration 7 years, and average LAI 8.4. The mean JSW at the narrowest point was 3.7 mm. The study was completed by 100 patients (85.5%). The reasons for premature withdrawal were adverse reactions in 15 (12.8%) and patient decision in 2 (1.7%).

Table IV
Change in Kellgren–Lawrence stage of the knee recorded at final visit

Baseline	0	1	2	3	4	Total
GP-C						
0	4					4
1		18	1			19
2			20	6		26
3				44	12	56
4					33	33
Total	4	18	21	50	45	138
Statistics	Value	ASE			95% CI	
κ	0.811	0.041			0.731	0.891
Baseline	0	1	2	3	4	Total
Placebo						
0	3					3
1		14	2	1	1	18
2			15	4	1	20
3			2	47	18	67
4					31	31
Total	3	14	19	52	51	139
Statistics	Value	ASE			95% CI	
κ	0.704	0.049			0.608	0.800

Test for equal κ (GP-C) and κ (placebo), *P*=0.094.

HIP: JSN

Results of the primary efficacy variable for the hip are recorded in Table VI. As with the knee, there was no difference in the progression of JSN between the GP-C and placebo groups. The change in Kellgren–Lawrence grade is recorded in Table VII. In those with hip OA, there were no more frequent changes into higher stages with those on GP-C than those on placebo (*P*=0.44).

A subset analysis of those with hip OA completing the study with an initial JSN of ≥1 mm and at least a Kellgren–Lawrence grade of 2 included 25 from the GP-C group and 21 from the placebo group. JSW was reduced from 3.29±0.15 to 3.06±0.17 mm (change −0.23±0.14 mm) in GP-C group and from 3.31±0.27 to 2.73±0.26 in placebo group (change −0.58±0.16 mm). There was no significant difference but a trend in favor of GP-C (*P*=0.11).

The changes in JSW from hip OA in yearly intervals are demonstrated in Table VIII. There are no differences in values between the study groups in any year. In contrast to the knee study groups, the decrease of JSN was most rapid in the last 3 years. The mean annual JSN was 0.045 mm in the GP-C group and 0.11 mm in the placebo group.

The number of patients who progressed >0.5 mm in the 5 years was 6/25 (24%) in the GP-C group vs 13/21 (62%) in the placebo group.

SECONDARY OUTCOME VARIABLES

The knee LAI index decreased 0.56±0.31 points in the GP-C group in contrast to a decrease of 1.53±0.32 points

Table V
Change in knee joint space (mm) in yearly intervals (subset of patients with Kellgren–Lawrence ≥2 and JSW>1 mm, completers)

	GP-C (*N*=86)	Placebo (*N*=95)	Significance
Baseline	4.31±0.14	4.14±0.14	NS
1 year	3.96±0.15	3.84±0.14	NS
2 years	3.92±0.15	3.76±0.14	NS
3 years	3.86±0.15	3.72±0.14	NS
4 years	3.74±0.16	3.59±0.15	NS
5 years	3.81±0.18	3.64±0.16	NS
Δ change	−0.49 mm	−0.50 mm	NS

GP-C Rumalon®.
Data are mm±S.E.M.
There are no statistical differences between GP-C and placebo.

Table VI
Change in hip joint space between GP-C and placebo groups

Study group	Baseline (mean±S.E.M.)	End point		Change (mean±S.E.M.)
		Raw (mean±S.E.M.)	Adjusted (mean±S.E.M.)	
GP-C	3.60±0.16	3.39±0.19	3.50±0.08	−0.21±0.08
Placebo	3.80±0.17	3.58±0.20	3.47±0.08	−0.22±0.08
Difference	0.20±0.24		0.03±0.12	0.01±0.12
95% CI	[−0.67; +0.66]		[−0.20; +0.25]	[−0.22; +0.24]
P (1) value	*P*=0.39		*P*=0.82	*P*=0.91
P (2) value	*P*=0.37		*P*=0.72	*P*=0.53

P (1): Difference between GP-C and placebo groups; parametric evaluation (two sided *t*-test).
P (2): Difference between GP-C and placebo groups; non-parametric evaluation (Wilcoxon test).

Table VII
Change in Kellgren–Lawrence stage of the hip recorded at final visit

Baseline	0	1	2	3	4	Total
GP-C						
0	7	1				8
1		16		1		17
2			5	1		6
3		1		18	3	22
4					5	5
Total	7	18	5	20	8	58

Statistics	Value	ASE	95% CI	
κ	0.837	0.058	0.724	0.950

Baseline	0	1	2	3	4	Total
Placebo						
0	10					10
1	1	20				21
2		1	5	2		8
3				13	2	15
4					5	5
Total	11	21	5	15	7	59

Statistics	Value	ASE	95% CI	
κ	0.865	0.051	0.765	0.966

Test for equal κ (GP-C) and κ (placebo) *P*=0.442.

Table VIII
Change in hip joint space (mm) in yearly intervals (subset of patients with Kellgren–Lawrence ≥1 mm, completers)

	GP-C (*N*=25)	Placebo (*N*=21)	Significance
Baseline	3.29±0.15	3.31±0.27	NS
1 year	3.36±0.13	3.42±0.27	NS
2 years	3.29±0.15	3.25±0.27	NS
3 years	3.28±0.15	3.04±0.28	NS
4 years	3.21±0.17	2.94±0.30	NS
5 years	3.06±0.17	2.73±0.26	NS
Δ change	−0.23 mm	−0.52 mm	NS (*P*=0.11)

GP-C Rumalon®.
Data are mm±S.E.M.
There are no statistical differences between GP-C and placebo.

in the placebo group. Although statistically significant (*P*=0.04), the reduction of 0.93 points was not considered clinically relevant. For the hip, there was no change and no difference in change in the treatment groups of the LAI grades after 5 years.

There were no statistical differences between the study groups from baseline to end of study in changes in pain on passive motion for either knee OA (*P*=0.39) or hip OA (*P*=0.82).

There are no statistical differences in NSAID consumption between the study groups from baseline to end of study in knee OA (*P*=0.62) or hip OA (*P*=0.73).

ADVERSE EVENTS

Adverse events were uncommon. No serious adverse events were identified that were attributed to the GP-C. In general, reactions were mild and subsided quickly (Table IX). There were 59 (14.8%) cases of adverse events recorded. There were 29 (14.5%) cases in the GP-C groups and 30 (15.0%) cases in the placebo groups (NS). Adverse events leading to withdrawal from the study occurred in 17 (8.5%) of the GP-C groups and 16 (8.0%; NS) of the placebo groups.

Adverse reactions leading to withdrawals appeared mostly in the first 3 years (five in year 1, 13 in year 2, 12 in year 3) and less in the last 2 years (two in year 4, one in year 5). There were 13 deaths, evenly distributed between the treatment groups: malignancy (6), ischemic heart disease (3), pulmonary emboli (2), motor vehicle accident (2).

Discussion

In a 5-year prospective trial, there was no difference in progression of JSN between GP-C and placebo treatment for OA of hip or knee. Similarly, there was no difference between groups in secondary clinical outcome measures or in subgroup analyses. Given that patients were selected on the basis of having symptoms, we also failed to demonstrate any symptom benefit of GP-C over placebo. We were not able to confirm the results of prior studies performed by Catona[10] and Rejholec.[10] However, there are previous clinical trials that have demonstrated benefit from GP-C.[10,11] It may be that the effects of the GP-C were small and the measurements selected for the study were not sensitive enough to detect a difference between the placebo and the study drug.

This study was designed and initiated in 1989. More recent publications have described more exact techniques

Table IX
Adverse events

	GP-C (*N*)	Placebo (*N*)
Pain at injection site	5	19
Skin	8	10
Exanthema	2	2
Skin rash, eruption, rash	3	3
Erythema	2	0
Pruritus	1	4
Edema	0	1
Cardiovascular diseases	4	5
Acute myocardial infarction	2	1
Ischemic heart disease	1	2
Pulmonary embolus	1	1
Congestive heart failure	0	1
Cancer	3*	3+
Surgery	6	3
Knee replacement	2	0
Hip replacement	4	3
Gastro-intestinal system	0	2
Musculo-skeletal system	5	7
Rheumatoid arthritis	1	3
Pain of joint and muscle	4	4
Miscellaneous	7	3
Patients	29 (14.5%)	30 (15%)
Adverse events	38 (19%)	52 (26%)
Drop-out	17 (8.5%)	16 (8%)
Death	7 (3.5%)	6 (3%)

*Colon, prostate, leukemia.
+Colon, pancreas, lung.

for measuring joint space for both hip and knee.[16–22] Although the standing position for the knee is still recommended, positioning by fluoroscopy, the semi-flexed positioning of the knee, correction for magnification, the use of a foot map and digitization of the radiograph with computer measurement of joint space are examples of the refinement of radiographic techniques. In this study positioning was quite reproducible when the radiographs were compared; however, small changes might not have been detected for the reasons above.

Patient selection also has an influence on trial results. This study included patients with Kellgren–Lawrence stage I and stage IV; stage I might progress slowly, or not at all; it is probably not possible to show structure-modifying changes in those with stage IV disease. Current protocols for structure modification generally recommend studying only Kellgren–Lawrence stage II and III disease.[19] In this study, the evaluation of those with Kellgren–Lawrence stages II and III would probably result in a study with insufficient power to detect a difference.

There are several studies examining the rate of radiographic JSN.[23–26] Results of these studies vary from 0.06 to 0.6 mm/year, a 10-fold difference. More extensive study is needed as much of the present discrepancy may relate to the radiographic methods, patient selection and the period of observation. The results of this study point out the need for the continuing improvement of our imaging techniques. In this regard, we await the validation of magnetic resonance imaging,[27] as well as that of arthroscopy and surrogate biochemical markers.[28,29]

There are presently many agents being examined for structure modification in OA, such as chondroitin sulfate,[30] hyaluronate,[31] diacerrhein,[32] and glucosamine.[33] This study points out several of the difficulties in studying potential structure modifying agents. More recent studies are using refined radiographic techniques, but are studying the intervention for shorter periods of time, because it seems that much of the progression often occurs in the earlier years of a trial. Also, this study suggests that progression of disease in the non-treatment group may be slower than one would anticipate from the existing literature. Investigators need to be aware, and plan accordingly.

The lack of effect in this study raises concern that JSN may not be the ideal measure for disease progression in OA. An alternative is to use an atlas of standard images.[16] Although not as quantitative as the above techniques, the atlases examine the entire joint and not just the thickness of the articular cartilage.

In summary, there was a slow progression of JSN in this study of OA of the hip and knee over a 5-year period in a cohort of 400 patients. In this setting, GP-C failed to demonstrate structure modification.

Acknowledgments

The authors would like to thank to Dr Francois Bailleul, Jean-Philippe Combal (Pierre Fabre Médicament) for their helpful contributions to this work. We are also much indebted to Dr F. Cabrieres (DCI, Bougival), Dr P. de Tonquedec (Octant, Marly-le-Roi), and Dr J. M. Grouin for data monitoring and statistical analysis.

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