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Original Article

Systems to Assess the Progression of Finger Joint Osteoarthritis and the Effects of Disease Modifying Osteoarthritis Drugs

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Abstract: Our objective was to assess the progression of osteoarthritis (OA) using scoring systems based on the anatomical changes recorded in the finger joints on standard radiographs and to test how far these scoring systems could be used to evaluate the effects of candidate 'disease modifying osteoarthritis drugs' (DMOAD). The appearance and growth of osteophytes, narrowing of the joint space and subchondral bone changes allowed the classic OA-associated anatomical lesions to be used to score the progression of finger joint OA. Progression of OA in the finger joints was also assessed by the their evolution through previously described and predictable anatomical phases on standard X-rays. These phases were characterised by complete loss of the joint space preceding or coinciding with the appearance of subchondral cysts eroding the entire subchondral plate, and have been described in 'inflammatory' or 'erosive' OA. The erosive episodes were followed by processes of remodelling. In order to interfere with the progression of osteoarthritis, two chondroitin sulphates with possible DMOAD effects were used in two series of patients with OA of the finger joints. The patients were included in two separate randomised, double-blind placebo-controlled trials: 46 of them received chondroitin polysulphate and 34 received chondroitin sulphate. Eighty-five patients were kept on placebo medication and were used as controls. All 165 patients were followed for 3 years. Postero-anterior X-rays of the metacarpophalangeal and interphalangeal (IP) finger joints were obtained at the start of this prospective study and at yearly intervals thereafter. Almost 80% of the distal IP and 50% of the proximal IP were affected at study entry. In approximately 40% of the patients the classic picture of OA of the IP joints was complicated by manifest erosive OA changes. The two systems to score the progression of OA (Anatomical Lesion and Anatomical Phase Progression Score System) showed definite progression within 3 years of follow-up, especially in the IP joints. When compared with the placebo controls, none of the chondroitin sulphates prevented OA from occurring in previously normal finger joints. However, when the classic OA-associated anatomical lesions were considered, OA was less progressive in both active treatment groups. Furthermore, fewer patients from both chondroitin sulphate- and chondroitin polysulphate-treated groups developed 'erosive' osteoarthritis. In conclusion, conventional radiographs can be used to assess the morbidity and progression of hand OA. The systems used to score the progression of finger joint OA allowed the DMOAD effects of both chondroitin sulphates to be evaluated. The data recorded during these pilot studies should help investigators to design future long-term clinical experiments.

Keywords: Chondroitin sulphates; Disease-modifying osteoarthritis drugs; Finger joints; Osteoarthritis

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Introduction

Single bilateral posteroanterior (PA) hand radiographs are considered sensitive enough to assess the radiological progression of the anatomical lesions in osteoarthritic (OA) finger joints [1,2]. These documents allow for the changes in the numbers of affected distal interphalangeal (DIP), proximal interphalangeal (PIP) and metacarpo-

phalangeal (MCP) joints per subject to be studied. The anatomical progression of the disease over years can be recorded through the appearance and changes in specific anatomical features, e.g. osteophytes, joint space width, subchondral cysts or sclerosis, which are associated with the classic non-erosive type of OA.

About half of the patients who consult their physician with symptomatic hand OA appear to develop a destructive type of OA of their finger joints. We have reported the anatomical evolution of hand OA in a population consisting almost exclusively of women who sought medical advice for symptomatic OA and who reported first symptoms early in the fifth decade of life [3]. The disease was characterised by inflammatory episodes and by a rapidly developing symmetrical involvement of the finger joints. The clinical picture and the radiographic lesions were identical to those described as 'menopausal' [4], 'inflammatory' [5,6] or 'erosive osteoarthritis' [7–9] of the finger joints. Destructive changes precede a period in which repair phenomena lead to the generation of a new subchondral plate covered by cartilaginous tissue. Huge osteophytes are responsible for the nodular aspect of the affected finger joints. This erosive form of OA affects both PIP and DIP joints. It has been concluded that all clinically manifest Heberden's and Bouchard's nodes with clinical and radiological evidence of hard tissue enlargement [10,11] go through this destructive erosive phase.

It has been generally accepted that damage sustained by either articular cartilage or subchondral bone may lead to the development of OA. Within certain limits, articular cartilage cells are capable of restoring cartilage damage. Articular cartilage chondrocyte metabolism changes during adult life. Declining aggrecan synthesis rates and a decreased capability to assemble large molecular size aggregates with increasing age in human articular cartilage have been reported [12–21]. The impaired assembly of large molecular size aggregates may be the consequence of a problem with the synthesis of highly polymerised hyaluronan filaments [22]. These findings illustrate a progressive failure of mature articular chondrocyte repair function in humans and may account for the increasing incidence of OA in an aged population.

Modulation by exogenous glycosaminoglycans and other polysaccharides of hyaluronan and proteoglycan metabolism of connective tissue cells has been repeatedly reported in the literature [23–33]. Human articular chondrocytes in vitro responded with an increased synthesis of highly polymerised hyaluronan [30] and of aggrecan in monomeric form, and in aggregates when chondroitin (poly)sulphates were added to the culture medium [31,33]. Electron microscopic studies confirmed the immobilisation of higher numbers of aggrecans on longer hyaluronan filaments synthesised by differentiated human cartilage cells exposed to chondroitin polysulphate and other sulphated polysaccharides [33].

Considering their effects on connective tissue cell repair mechanisms, sulphated polysaccharides, e.g. chondroitin sulphate and chondroitin polysulphate, may modify the disease process in OA and therefore may possess disease modifying osteoarthritis drug (DMOAD [34,35]) effects. In order to assess these effects on the retardation of the progression of osteoarthritis, both chondroitin sulphates were used in a double-blind placebo-controlled long-term study. The study population consisted of patients with osteoarthritis of the finger joints, a condition the anatomical progression of which over years can be assessed using standardised methods [3]. The primary variable in this study was the anatomical progression of the disease as evaluated on the X-rays. The data recorded during these pilot studies should help investigators to design future long-term clinical experiments.

Patients and Methods

Two randomised double-blind placebo-controlled studies were successively and independently performed to assess the effects of chondroitin sulphate and of chondroitin polysulphate as 'disease modifying osteoarthritis drugs' (DMOAD). Patients were included in four treatment groups: the chondroitin polysulphate-treated group (CPS) and their placebo controls (Pl-CPS) for the first study; the chondroitin sulphate-treated group (CS) and their respective placebo controls (Pl-CS) for the second study. None of the patients were participating in both treatment arms. Randomisation of the study medication was done in blocks of four and successive treatment allocation numbers were administered following the order of inclusion. All patients were recruited and followed by the three authors in the department of Rheumatology of the Ghent University Hospital, and gave their informed consent before study entry.

Patient Selection Criteria

Patients between 40 and 70 years of age and with symptom-producing osteoarthritis (OA) of the finger joints were selected. The diagnosis of OA was confirmed according to the presence of osteophytes and/or joint space narrowing with or without subchondral sclerosis on conventional X-rays of the hands [1]. For both trials, a 2-year inclusion period was allowed to introduce the reported numbers of patients. Sample size calculation was not possible, as previous studies allowing the progression of finger joint OA to be estimated were not available. All patients were Caucasian and had sought medical advice for incipient inflammatory symptoms in and around the distal (DIP) and proximal (PIP) interphalangeal joints. As the currently conventional algofunctional indices were not in use at the start of these studies, the patient's general opinion about their clinical condition at entry was assessed in a one-sentence question ('How is the osteoarthritis that is causing pain and stiffness of your finger joints interfering with your daily activities?') and reported on one 100 mm visual

analogue scale. Other rheumatic conditions were excluded by history taking and clinical, X-ray and laboratory investigations. All patients were negative for rheumatoid or antinuclear factor. During the study, the patients were dissuaded from taking non-steroidal anti-inflammatory drugs (NSAIDs) for periods longer than 2 weeks.

Drugs and Drug Administration

The chondroitin polysulphate used in this clinical study (Arteparon, Luitpold Werk, Munich) was purified bovine chondroitin sulphate which had been chemically sulphated. The preparation had an average molecular weight of 6000 Da and each chondroitin disaccharide unit carried three to four sulphate groups [36]. Repeated intramuscular injections of 125 mg of the drug in humans resulted in tissue concentrations of 1 μg/g cartilage [37]. Patients in the CPS group received 50 mg of chondroitin polysulphate, administered intramuscularly twice weekly for 8 weeks every 4 months. Patients in group Pl-CPS received 1 ml of placebo (saline) by the same schedule and route of administration.

The chondroitin sulphate used in the trial was a purified blend of chondroitin-4-sulphate and chondroitin-6-sulphate disodium salts (Condrosulf, IBSA; Lugano). The extremes of molecular weight for the chondroitin sulphate in this preparation were 15 000 and 50 000 Da (average 30 000 Da). Pharmacokinetic studies with chondroitin sulphates with an average molecular weight of 7500 and 14 000 Da, [38,39] in various laboratory animal models and humans have demonstrated that 5%–10% of a single oral dose of the preparation reached the body tissues over a period of 48 h and still had the molecular characteristics (MW and sulphation) required to elicit biological effects. Following oral administration, the chondroitin sulphate recovered in the serum was found to be partially depolymerised (molecular weights <5000 Da). The degree of sulphation was merely reduced by 15%–20% [40]. About 10% of the material excreted in the urine could still be precipitated with quaternary ammonium salts, indicating retention of the sulphate groups. Patients in the CS or Pl-CS groups received a capsule containing 400 mg of chondroitin sulphate or a placebo capsule (Lactose-Monohydrate, 500 mg) three times daily throughout the 3 years.

X-rays

Posteroanterior (PA) X-rays of both hands, with the third digit in the axis of the forearm, were obtained at the start of the prospective studies and at yearly intervals thereafter. As the interphalangeal (IP) and metacarpophalangeal (MCP) joints of the thumb were found to be in oblique positions on these films, the thumb joints were not considered in the evaluation. Consequently, 24 joints: DIP, PIP and MCP 2, 3, 4 and 5 of both hands (8 DIP, 8 PIP and 8 MCP joints) per X-ray, were studied. This enabled the investigators to define the frequency of OA of these joints at the start of these studies and to quantify the increase of prevalence of OA during consecutive years in previously normal joints in the four groups; and to document the radiological progression in the pathologic finger joints over a 3-year period. When X-rays were compared at 1-year intervals, it was found that the minute changes were too often disputable. Hence, only the PA X-rays obtained at the start of the study and after 3 years were used for evaluation.

Scoring Systems

Two scoring systems were used to quantify the anatomical progression of finger joint OA according to previously published methods [3].

Anatomical Lesion Progression System: This scoring system was based on the changes in the anatomical lesions classically attributed to OA: changes in osteophytes or small ossification centres occurring at the joint margins, joint space narrowing and subchondral bone cyst formation. Subchondral sclerosis was not considered, as it was difficult to quantify. The condition at the time of study inclusion was compared with the appearance 3 years later. Points were attributed to changes in the aforementioned items, as illustrated in Table 1. The scores for eight DIP, PIP and MCP joints were combined for each patient. Disease progression was more obvious in the DIP and PIP joints. Therefore, differences between groups in the Anatomical Lesion Progression Scores of the 16 IP finger joints were also calculated.

Table 1. Scores attributed to changes in osteoarthritic joints

Osteophytes*		Joint space		Subchondral cysts	
Appearance	+1.0	Narrowing	+1.0	Appearance	+1.0
Disappearance	–1.0	Widening	–1.0	Disappearance	–1.0
Increase in size	+0.5			Increase in size	+0.5
Decrease in size	–0.5			Decrease in size	–0.5

*Small ossification centres at the joint margins were regarded as OA-related changes and were evaluated as osteophytes.

Anatomical Phase Progression System: OA of the finger joints has been found to show destructive changes in the DIP and PIP joints [3,5–9,11]. These changes are characterised by complete loss of the joint space preceding or coinciding with the appearance of subchondral cysts eroding the entire subchondral plate. These episodes of destructive OA subsided spontaneously and were followed by processes of repair, as appeared from the follow-up. Five anatomical phases in the evolution of OA of the finger joint were defined, as illustrated in Fig. 1: the unaffected ‘N’ joint, the non-erosive stationary OA joint (‘S’ phase), the joint with a

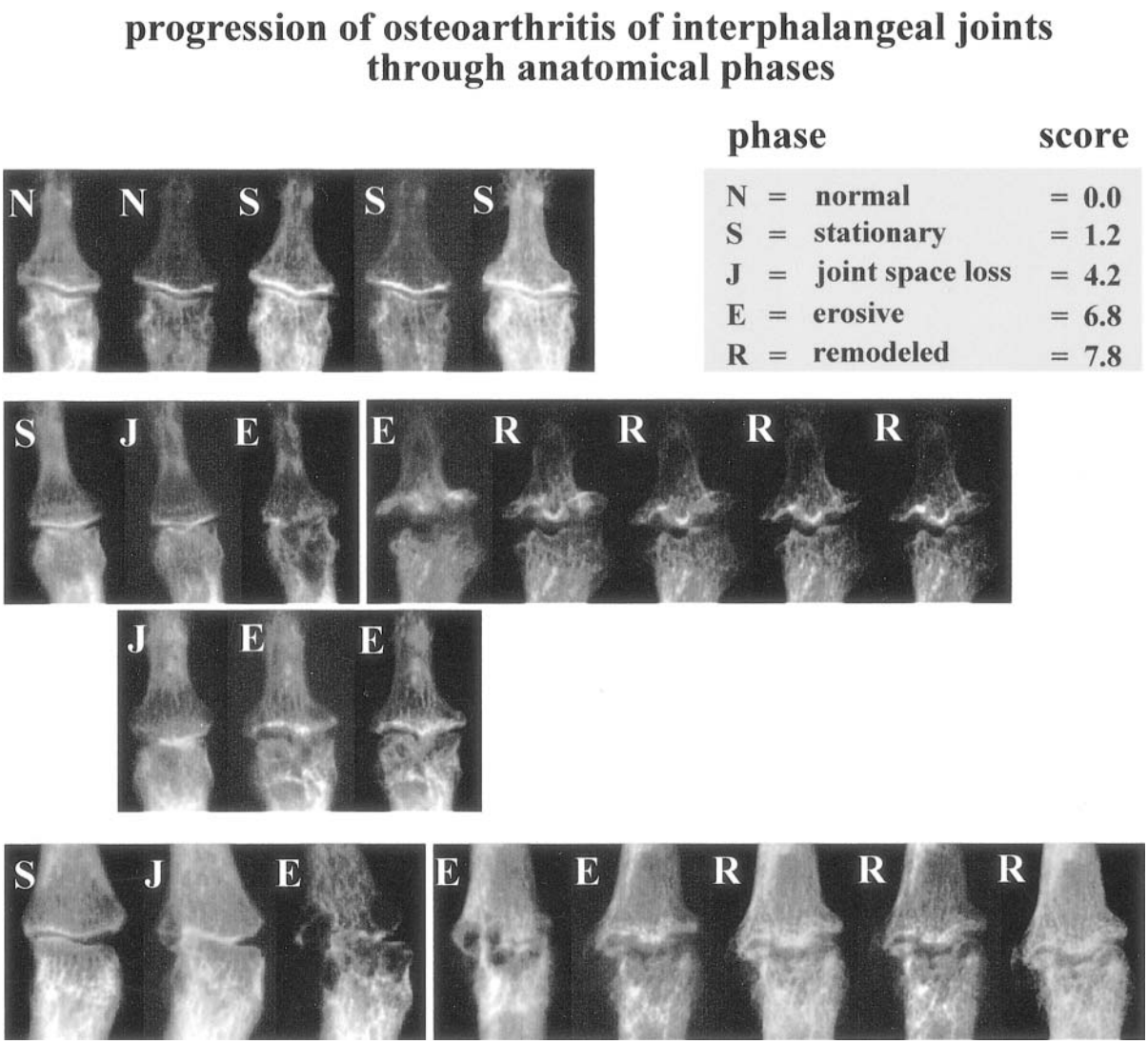

Fig. 1. Anatomical phases in the progression of OA of the finger joints. 'N'=non-affected joints. 'S'=stationary OA phase: classic appearance of OA. Small ossification centres and osteophytes are present at the joint margins. These can increase in size. Narrowing of the joint space can occur. 'J'=loss of joint space phase. After remaining for a variable time in the stationary phase, some joints (exclusively PIP or DIP) become destroyed. The joint space completely disappears within a relatively short period of time. 'E'=erosive phase: concurrently with or shortly after the disappearance of the articular cartilage, the subchondral plate becomes eroded. The appearance is that of a pseudo-enlargement of an irregular joint space. Destructive phases ('J' and 'E' phases) can last for 1 or more years and are always followed by repair or remodelling. 'R'=remodelling phase: new irregular sclerotic subchondral plates are formed, and in between these a new joint space becomes visible. Huge osteophytes are formed during this phase. The progression through these phases in four different DIP joints is shown in the three upper rows. The evolution in two different PIP joints is shown in the bottom row. X-rays were taken at 1-year intervals. Numerical values attributed to the respective phases [28] are given in the figure.

disappeared joint space ('J' phase), the joint showing erosive lesions ('E' phase) and the remodelled 'R' joint. The recognition of these phases enabled the investigators to devise a scoring system for the X-ray evolution of OA of the finger joints. Arbitrary numerical values were attributed to each of these phases as previously reported [3] and are presented in Fig. 1. For each patient, the phase values were summed for the eight DIP, PIP and MCP joints to obtain a score for the anatomical phases. Values at the start were compared to scores attributed after 3 years. As it appeared, progression through the anatomical phases occurred almost exclusively in the DIP and PIP joints. Therefore, also the Anatomical Phase Scores of the 16 IP joints of each patient were calculated to assess differences between groups at the start and after 3 years of follow-up.

Comparison of Different Study Groups at Inclusion

The following variables were studied to ascertain the comparability of the groups (both placebo groups and

treated cohorts) at entry in terms of incidence and morbidity of the disease: the number of DIP, PIP and MCP joints involved per patient; the number of patients presenting at least one DIP or PIP joint in a destructive (J,E) or remodelled (R) phase; the numerical values accorded to the anatomical phases of each patient's eight DIP, PIP and MCP joints.

Assessment of Disease Progression

Disease progression over 3 years of follow-up was evaluated using the following variables : the development of OA in previously unaffected joints was studied by assessing the numbers of DIP, PIP and MCP joints involved per patient at the start and 3 years later; the progression of OA in the finger joints in the respective groups over the 3-year period was studied using the two numerical scoring systems for the morbidity of the disease: the Anatomical Lesion Progression System and the Anatomical Phase Progression System; and the individual patient's risk to develop or to worsen 'erosive osteoarthritis' was also assessed.

Assessment of Individual Patients' Risk of Developing or Experiencing Progressive Erosive OA

Individual patients' risk of developing erosive OA was determined by assessing the number of patients presenting exclusively non-erosive OA joints ('N' or 'S' phases) at study entry, of which at least one IP joint progressed to a destructive phase ('J','E') over a 3-year period. Progression of erosive OA was evaluated by looking at the number of subjects suffering from erosive OA at study entry, and whose joints showed further progression through these destructive phases during follow-up.

Statistical Analysis

Intrareader assessments were done by both readers separately, scoring the X-rays twice with a 1-month interval between the two readings. The changes in the anatomical lesions were quantified without the readers knowing their chronological sequence. Anatomical phases were analysed with the readers knowing the chronological order of the documents, as the definition of an anatomical phase is not made by comparison of X-rays. For dichotomous variables (presence/absence of OA, definition of specific anatomical phases), percentage agreement and weighted κ statistics were chosen to assess intra- and interreader reliability. The use of κ statistics posed some problems when a scale with multiple categories was used; therefore, the reliability of the assessments of the anatomical progression scores was tested by calculating the correlation coefficients between values obtained by both readers.

Intra- and interreader agreement was previously assessed on the DIP and PIP joints on the PA X-rays of the right hand of 20 subjects (160 joints) of the PI-CPS group (3) and reported to be excellent for the dichotomous variables. Agreement on the changes in the anatomical lesions was acceptable. Interreader reliability was retested the same way on the DIP, PIP and MCP joints of both hands of 25 patients from this study (600 joints) and similar agreement was obtained (Table 2).

Wilcoxon's rank sum test was used to compare the incidence of OA in, and the Anatomical Phase Scores of, the DIP, PIP and MCP joints in the respective treatment

Table 2. Intra- and inter-reader reliability of systems for grading osteoarthritis of the finger joints

	Number of OA joints	Pathological phase	Anatomical scores	
Intrareader				
I % agree	81.9	93.1	corr coef	0.934
w.κ	0.623	0.831	R^2	87%
95% C.I.	0.294–0.952	0.261-1.401		
II % agree	86.9	84.4	corr coef	0.666
w.κ	0.726	0.645	R^2	44%
95% C.I.	0.327–1.125	0.284-1.005		
Inter-reader – first study/assessment				
% agree	86.3	80.6	corr coef	0.744
w.κ	0.726	0.595	R^2	55%
95% C.I.	0.338–1.114	0.253–0.937		
Inter-reader – second study/assessment				
% agree	92.3	85.0	corr coef	0.815
w.κ	0.815	0.702	R^2	66%
95% C.I.	0.681–0.945	0.574–8.835		

Number of OA joints and pathological phases: results of κ statistics. Readers: I= GV; II= EMV;
% agree: % agreement; w.κ and 95% CI: weighted κ and 95% confidence interval.
Anatomical scores: results of simple regression analysis: corr coef: correlation coefficients between values obtained by both readers. R^2: R-squared.

groups at the start of the study and after 3 years. This test was also used to compare the increases in Anatomical Lesion Progression Scores over 3 years in placebo and treated groups. χ^2 tests were used to compare proportions of patients showing destructive OA at study entry, and to compare the proportions of non-erosive OA patients in the study groups who developed erosive OA during follow-up. The same statistical method was used to study the proportions of patients presenting shifts in the anatomical phases of their finger joints during follow-up.

An endpoint analysis, instead of an intention-to-treat analysis, was done as most of the patients who discontinued the study did so during the first year, before follow-up X-ray documents were obtained. Outcome evaluation was thus done on the PA X-rays obtained at the start and at the end of 3 years of follow-up.

Results

One hundred and thirty patients with OA of the finger joints were enrolled in the study comparing chondroitin polysulfate (CPS: 66 patients) with placebo (Pl-CPS: 64 patients) and 92 in the study comparing chondroitin sulphate (CS: 44 patients) with placebo (Pl-CS: 48 patients). No significant differences were found between the four groups when demographic characteristics were compared (Table 3).

Forty-six patients in the CPS and Pl-CPS groups completed the 3-year double-blind trial. Thirty-four patients in the CS and 39 patients in the Pl-CS group completed the second trial. The reasons for withdrawal are given in Table 4. There were no significant differences between the number of and the reasons for the withdrawals from both studies. It is noteworthy that the large majority of withdrawals from the CPS/Pl-CPS

Table 3. General characteristics of the study population

Group	CPS	Pl-CPS	CS	Pl-CS
Number	66	64	44	48
Females	60	62	40	42
Males	6	2	4	6
Age*	55.2 ± 6.7	56.1 ± 9.2	57.6 ± 7.1	55.9 ± 8.9
Disease duration*	6.0 ± 3.6	7.3 ± 3.5	5.5 ± 3.5	5.7 ± 3.4
Subjective complaints*	44.5 ± 24.8	44.3 ± 25.0	35.2 ± 23.2	41.6 ± 24.2

*mean ± 1SD.

Table 4. Chondroitin sulphate- and polysulphate-treated groups versus respective placebo controls: patients included and withdrawn

	CPS	Pl-CPS	CS	Pl-CS	Totals
Patients randomised	66	64	44	48	222
Patients completing 3 years	46	46	34	39	165
Total withdrawn	20	18	10	9	57
during first year	33		19		52
after the first year	5		0		5
Patients withdrawn due to:					
adverse experience	0	0	1	0	
desired to be withdrawn*	12	9	4	3	
non-compliance with dosing	2	3	2	4	
lost to follow-up	5	3	2	2	
intercurrent diseases	1	1	0	0	
evolution to inflammatory RhD	0	2	1	0	
moved to another country	1	1	0	0	
Interphalangeal Joint Anatomical Phase Score at start					
Patients completing 3 years:					
M	10.4	15.2	15.6	16.8	
L-U	5.8–17.8	10.4–25.9	1.0–19.4	11.6–23.5	
Patients withdrawn:					
M	11.6	12.7	10.4	12.3	
L-U	4.1–23.3	4.6–18.5	5.8–27.9	4.6–27.8	
Subjective complaints at start					
Patients completing 3 years†	41.6±23.1	45.2±25.9	35.3±23.1	36.4±19.7	
Patients withdrawn†	50.1±27.3	42.4±23.7	35.1±23.7	48.2±27.7	
Duration of disease					
Patients completing 3 years†	6.5±3.6	7.5±3.5	5.2±3.5	5.2±3.3	
Patients withdrawn†	5.1±3.4	6.9±3.6	6.0±3.4	6.3±3.5	

CPS, chondroitin polysulphate; Pl-CPS, placebo of the chondroitin polysulphate trial; CS, chondroitin sulphate; Pl-CS, placebo of the chondroitin sulphate trial; RhD, rheumatic diseases. M, median; L-U, lower – upper quartile. *These patients felt that the therapeutic effort did not match the clinical discomfort resulting from their condition. †mean ± 1SD.

trial, and all those from the CS/Pl-CS trial occurred during the first year. Obviously, the major reason for treatment discontinuation was that patients subsequently decided not to put in so much effort into these 3-year clinical studies. The number of withdrawals for this specific reason was no different in the treated groups and their respective placebo controls. A serious gastritis was the reason for withdrawal of the one patient treated with CS. No patient was withdrawn for side-effects in the CPS study. Patients who completed the 3 years of follow-up, and those who decided to withdraw from the study, showed no differences when disease-associated variables such as duration of the disease, subjective complaints, and the Anatomical Phase Score of their IP joints at their inclusion in the study, were considered (Table 4).

Evaluation of the Study Populations at Entry

Comparison of Both Placebo Groups: The numbers of DIP, PIP and MCP joints involved in each patient in both placebo groups were compared by Wilcoxon's test for unpaired samples (Fig. 2). Both placebo groups did not differ at the DIP and the PIP level for this variable.

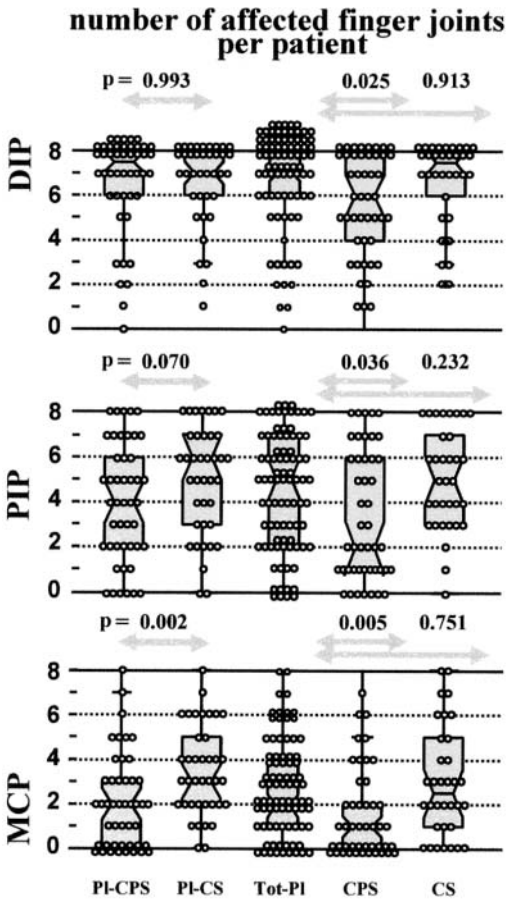

Fig. 2. Number of affected DIP, PIP and MCP joints at the patient's inclusion in the study. Differences (*P* values) between the respective study groups are shown: Pl-CPS versus Pl-CS; Tot-Pl versus CPS and CS. Patients' DIP and PIP joints were predominantly involved.

Table 5. Number of patients with 'destructive' interphalangeal joint OA at start

	No.	%			χ^2	*P*
Pl-CPS	22	47.8				
Pl-CS	14	35.9			0.790	>0.050
ToT-Pl	36	42.3				
CPS	11	23.9			4.725	<0.050
CS	12	35.3			0.252	>0.050

However, in the Pl-CS group more MCP joints were affected per patient than in the Pl-CPS group. The number of patients presenting at least one DIP or PIP joint in a destructive (J,E) or remodelling (R) phase at the start was not significantly different in both placebo groups (Table 5). MCP joints were not taken into account for this variable, as the number of MCP joints that were erosive at the start was extremely low (one J phase in the Pl-CPS group and no J or R joints in the Pl-CS group). The Anatomical Phase Scores of each patient's 8 DIP, 8 PIP and 8 MCP joints were calculated (Table 6). No significant differences were found between the Anatomical Phase Score of DIP and PIP joints of the patients in both placebo groups. MCP joints scored significantly lower in the Pl-CS group. The evaluation of the X-rays at study entry allowed us to conclude that both placebo groups were no different. The placebo patients were thus combined in a 'total placebo group' (Tot-Pl).

Comparison of CPS, CS-treated and Tot-Pl Groups

Identical variables to those used for the comparison of the two placebo groups were considered.

1. Comparison of the numbers of DIP, PIP and MCP joints affected in each patient in Tot-Pl, CPS and CS groups was performed by the Wilcoxon's rank sum test. No significant differences were noted between the CS and Tot-Pl groups. Fewer DIP, PIP and MCP joints were found to be affected in the CPS group (Fig. 2).
2. Numbers of patients presenting at least one DIP or PIP joint in a destructive (J,E) or remodelling (R) phase at their inclusion (Table 5) were not different in CS and Tot-Pl groups. However, the patients in the CPS group presented fewer joints in destructive phases than the patients of the Tot-Pl group.
3. The Anatomical Phase Scores of the 8 DIP, 8 PIP and 8 MCP joints of the patients in the Tot-Pl, CPS and CS groups are given in Table 6. The CS group did not present significant differences from the Tot-Pl group when this variable was considered. However, the CPS-treated patients were less affected at the start than those in the Tot-Pl group. No differences were observed for the MCP joints.

Table 6. DIP, PIP and MCP joint anatomical phase scores at start

	n		Average	Median	LQ–UQ	
Pl-CPS	46	DIP	15.0	9.3	8.1–21.5	
		PIP	6.8	4.6	2.3–8.1	
		MCP	2.5	2.3	0.0–3.5	
						Differences Pl-CPS vs Pl-CS
Pl-CS	39	DIP	12.2	9.3	8.1–15.9	DIP: $p = 0.586$
		PIP	7.0	7.0	3.5–8.1	PIP: $p = 0.155$
		MCP	4.0	3.5	2.3–5.8	MCP: $p = 0.002$
Tot-Pl	85	DIP	13.7	9.3	8.1–17.9	
		PIP	6.9	5.8	2.3–8.1	
		MCP	3.2	2.4	1.6–4.6	
						Tot-Pl vs CPS
CPS	46	DIP	9.3	7.0	4.6–9.3	DIP: $p = 0.002$
		PIP	4.3	2.3	1.6–7.0	PIP: $p = 0.019$
		MCP	2.0	1.6	0.0–3.5	MCP: $p = 0.060$
						Tot-Pl vs CS
CS	34	DIP	10.8	9.3	7.0–14.8	DIP: $p = 0.191$
		PIP	6.0	6.4	3.5–9.3	PIP: $p = 0.418$
		MCP	3.5	2.9	1.2–5.8	MCP: $p = 0.759$

Progression of OA over 3 Years of Follow-Up

Differences in disease progression in the three groups were assessed. There were no significant increases in the numbers of affected DIP, PIP and MCP joints during 3 years of follow-up in any of the groups. There were also no differences between treated and placebo groups (Fig 3).

The Anatomical Lesion Progression Score in individual patients is given in Table 7. Values for DIP, PIP and MCP joints in the CPS- and CS-treated groups were compared with the those of the Tot-Pl group. The Anatomical Lesion Progression Score in CPS-treated patients was significantly lower than in the Tot-Pl group. There were no significant differences between the CS group and the Tot-Pl group. Disease progression was more obvious in the DIP and PIP joints. Therefore, differences between groups in the anatomical progression score of the 16 interphalangeal finger joints were calculated. Interphalangeal joint OA progression scores over 3 years significantly decreased in the CPS-treated patients, whereas CS treatment seemed less effective (Fig. 4).

The Anatomical Phase Progression Score in individual patients is given in Table 8. Progression through the anatomical phases was not significantly different in the CPS, CS and Tot-Pl groups. Progression through the anatomical phases occurred almost exclusively – and in an identical manner – in the interphalangeal joints. Therefore, differences between groups in the Anatomical Phases Progression Scores of the 16 interphalangeal joints were calculated. Interphalangeal joint progression through anatomical phases over 3 years significantly decreased in the CPS-treated patients, whereas CS treatment showed a tendency to retard disease progression (Fig. 5).

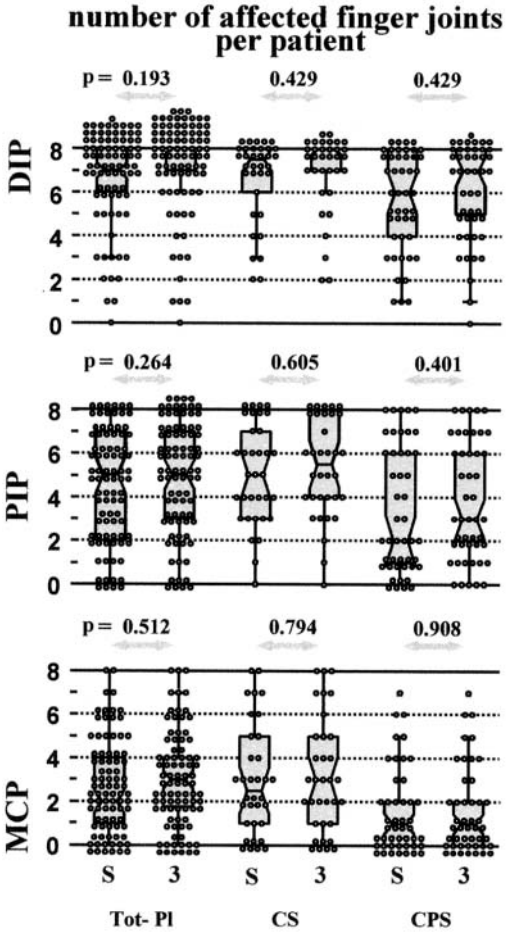

Fig. 3. Number of osteoarthritic DIP, PIP and MCP joints per patient in the placebo group (Tot-Pl) and in the CS- and CPS-treated groups. Notched box-and-whisker plots represent median values, upper and lower quartiles. Differences (*P* values) between the condition at the start of the study (S) and after 3 years (3) of follow-up are given.

Table 7. Anatomical lesion progression scores during 3 years of follow-up

		Average	Median	LQ–UQ	*P* value Tot-Pl vs. CS/CPS
DIP	Tot-Pl	3.5	2.5	1.0–4.5	
	CS	2.6	2.0	0.0–4.5	0.155
	CPS	2.2	1.0	0.5–3.0	0.013
PIP	Tot-Pl	2.8	2.0	0.5–3.5	
	CS	2.3	1.0	0.0–3.5	0.373
	CPS	0.8	0.5	0.0–1.0	0.00005
MCP	Tot-Pl	0.5	0.0	0.0–1.0	
	CS	0.4	0.0	0.0–0.5	0.702
	CPS	0.1	0.0	0.0–0.0	0.0024

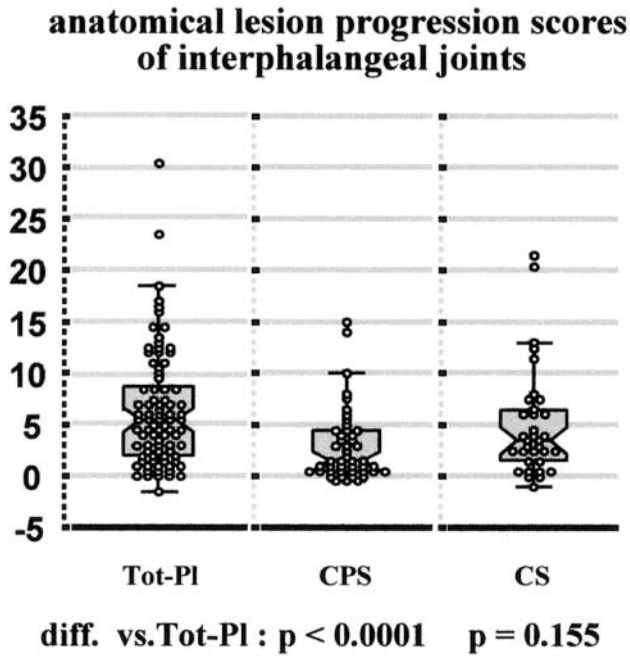

Fig. 4. Anatomical Lesion Progression Scores over 3 years of follow-up of the interphalangeal (DIP and PIP) joints of each patient. Notched box-and-whisker plots represent median values, upper and lower quartiles. Differences (*P* values) in progression scores between the placebo group (Tot-Pl) and the CPS- and CS-treated groups are given.

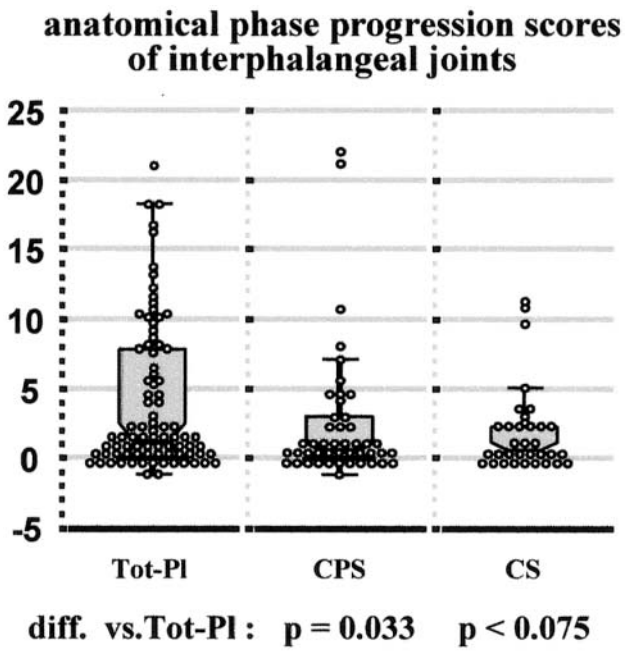

Fig. 5. Anatomical Phase Progression Scores over 3 years of follow-up of the interphalangeal (DIP and PIP) joints of each patient. Notched box-and-whisker plots represent median values, upper and lower quartiles. Differences (*P* values) in progression scores between the placebo group (Tot-Pl) and the CPS- and CS-treated groups are given.

Table 8. Anatomical phase progression scores during 3 years of follow-up

		Average	Median	LQ–UQ	*P* value Tot-Pl vs. CS/CPS
DIP	Tot-Pl	2.6	0.0	0.0–4.2	
	CS	1.5	0.0	0.0–2.5	0.365
	CPS	1.9	0.0	0.0–2.3	0.208
PIP	Tot-Pl	1.4	0.0	0.0–1.6	
	CS	0.4	0.0	0.0–0.0	0.016
	CPS	0.6	0.0	0.0–1.6	0.174
MCP	Tot-Pl	0.4	0.0	0.0–0.0	
	CS	0.2	0.0	0.0–0.0	0.717
	CPS	0.2	0.0	0.0–0.0	0.184

Individual Patient's Risk of Developing or Worsening 'Erosive Osteoarthritis'

Patients' risk of developing 'erosive OA' was searched for by assessing the number of patients presenting joints exclusively in 'stationary OA' phases (N or S) while included in the study, and developing a destructive phase (J,E) in at least one DIP or PIP joint over a 3-year period (Table 9). Seven of these patients out of 46 from the Tot-Pl group, progressed through destructive phases (J, E or R) in one or more IP joints. Only one patient out of 35, and two patients of the 34 with exclusively 'stationary' OA joints in the CPS- and CS groups, respectively, developed destructive phases. However, these differences were not significant.

Table 9. Number of initially 'non destructive' patients developing 'destructive' interphalangeal OA during follow-up

	n	Non-destructive at start	Development of destructive OA	Difference	
Tot-Pl	85	46	7		
CPS	46	35	1	χ^2=2.164	*P*>0.050
CS	34	24	2	χ^2=0.194	*P*>0.050

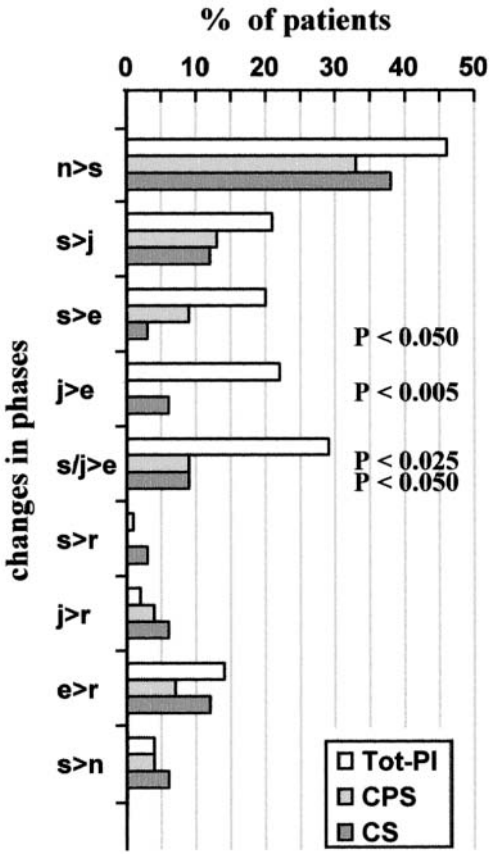

Fig. 6. Proportions of patients in the placebo group (Tot-Pl) and in the CPS- and CS-treated groups presenting a change in anatomical phase in an interphalangeal joint during the 3 years of follow-up. Differences (*P* values) in the proportions of patients in the respective groups (Tot-Pl versus CPS or CS) presenting a particular change are given. N=non affected; S=stationary OA; J=OA joint with disappeared joint space; E=erosive OA joint; R=remodelled OA joint.

Patients' progression through the different anatomical phases in the CPS, CS and Pl-Tot groups during the 3-year follow-up period is shown in Fig. 6. None of the treatments prevented the patients developing OA (N→S) in previously unaffected joints. New OA joints were seen in 45.9%, 38.2% and 32.6% of the patients in the CPS, CS and Pl-Tot groups, respectively. These differences were not significant.

Patients' risk of worsening their 'erosive OA' was evaluated by looking at the number of subjects whose joints showed further progression through the destructive phases during follow-up (Fig. 6). Progression to the erosive (E) phase in patients whose joints previously showed stationary OA or loss of the joint space (S or J phases) was significantly halted. 29.4% of the placebo-treated subjects developed frank 'erosive' osteoarthritis in previously stationary OA joints (S/J→E). In the CS- and CPS-treated groups, development of 'erosive' OA occurred in 8.8% out of 34, and in 8.7% out of 46 patients, respectively. An 'S→E' or a 'J→E' phase type of evolution occurred in 20.0% and 22.4% of the 85 placebo-treated patients, respectively. One (2.9%) and two (5.9%) of the CS-treated patients progressed through these phases. Four out of 46 (8.7%), and none of the 46 (0.0%) CPS-treated patients showed this phase type of evolution. Once in one of the destructive phases, the proportion of patients whose interphalangeal joints showed remodelling was not affected by either treatment.

Discussion

A scoring system to assess the progression of naturally occurring osteoarthritis (OA) of the finger joints has been proposed previously. Data on the incidence, morbidity and progression of OA of the finger joints in the Pl-CPS group have been reported in detail [3]. We have used the scoring system to study the comparability of different randomly selected populations with finger joint OA, and to explore the possible disease-modifying osteoarthritis drug (DMOAD) effects in these patients when treated with two chondroitin sulphates over a 3-year period. Symptomatic patients (pain, stiffness, hindrance when performing daily duties) have been shown to have more progressive osteoarthritis of their finger joints [41]. This was also reported for knee OA [42,43]. Therefore, only subjects with subjective complaints were entered, so as to select those with a higher risk of progression. The clinical data at the time of inclusion were thus recorded to exclude that some of the study groups contained more patients with more aggressive forms of OA. Clinical complaints were not followed during the study period.

It was considered that the study of both the interphalangeal joints and the MCP joints would give

enough information about the radiological progression of the two types of OA. The destructive evolution characteristic of what is classically coined as 'erosive' [9] or 'inflammatory' [5,6] osteoathritis of the finger joints is exclusively seen in the distal and proximal interphalangeal joints. MCP joints show a non-erosive type of evolution. 'Erosive' osteoarthritis is also seen in the interphalangeal (IP) joint of the thumb, whereas the MCP and carpometacarpal joints of the thumb show the 'non-erosive' form of the disease. However, the joints of the thumb were found to be in oblique positions on the AP films and were difficult to evaluate. Therefore, these joints were not taken into consideration. It was accepted that six more joints would not strengthen the conclusions obtained from a study of 24 other joints per X-ray.

During the study, 25% and 21% respectively of the patients withdrew from the CPS/Pl-CPS and CS/Pl-CS groups. These numbers are not unexpectedly high. There were no significant differences between the number of or the reasons for the withdrawals from both studies. It is noteworthy that the large majority of withdrawals occurred during the first year. Obviously, the major reason for treatment discontinuation was that patients subsequently decided not to put in so much effort during these 3-year studies. Patients who completed the 3 years of follow-up, and those who decided to withdraw from the study, showed no differences in either disease-associated variables or the morbidity scores of their finger joints at study inclusion. Consequently, these withdrawals did not induce unexpected biases in the starting conditions of the respective treatment groups. On the other hand, no 3-year assessment of the withdrawal group could be obtained and it cannot be confirmed that those who withdrew were no different from the placebo group on study completion.

After completion of the studies it appeared that the numbers of patients with 3 years of follow-up in the different trial arms were too small to allow proper statistical comparison between CS-treated, and CPS-treated patients and their respective placebo controls. It was shown that both placebo groups were similar apart from the number of affected MCP joints in the included patients. However, MCP joints do not greatly contribute to the progression scores in finger joint OA [3,5,6,9], as the erosive form of OA is not seen in these joints. It was thus decided to pool these patients in a larger 'total placebo group'. The use of one single placebo group offered the advantage of estimating and comparing the effect sizes of both treatments. Moreover, the pictures on the X-ray files are objective findings and could not have been influenced by the subjective feelings of the patient with regard to the route of administration of the drugs.

A 3-year follow-up enabled us to investigate the possible DMOAD effects of the two chondroitin sulphates. Chondroitin sulphate and chondroitin polysulphate have an identical polysaccharide backbone but their degree of sulphation is different. Both have profound and similar effects on the synthesis and turnover of the structural extracellular matrix compounds of human connective tissues, e.g. articular cartilage and synovial membrane [26–28,30–32,44], and may thus affect connective tissue repair. These polysaccharide (poly)sulphates have a 'tropism' for connective tissues such as cartilage [37–39,45,46], and at least chondroitin polysulphate was shown to have 'structure-modifying' properties in vivo [27,47].

This study did not allow us to conclude that chondroitin sulphate or chondroitin polysulphate treatment prevented patients with OA of the finger joints developing OA in previously unaffected joints. New OA joints were seen in the same proportions of the patients in both control and treated groups. The high proportions of joints involved at study entry, and the fact that changes in the anatomy of finger joints that become osteoarthritic during follow-up are often subtle, may render this variable less efficient to assess the effects of drugs on the progression of hand OA. However, the morbidity of the disease was significantly reduced in both treated populations. Progression of the anatomical lesions characteristic of OA, e.g. osteophytes, loss of the joint space and changes in the architecture of subchondral bone, was significantly less pronounced in the chondroitin polysulphate-treated patients than in the control group. The Anatomical Lesion Progression System allowed the retardation of the disease to be detected in the MCP, PIP and DIP joints of CPS-treated patients. This was not the case in CS-treated subjects.

Evolution through the destructive anatomical phases characteristic of 'erosive' or 'inflammatory' osteoarthritis of the finger joints was significantly reduced in both treatment groups. The Anatomical Phase Progression System did not allow MCP joints to be scored. The DIP and PIP joints had to be combined in one IP joint group to detect significant disease retardation under CPS treatment when this system was used. CS-treated subjects showed a tendency to progress at a slower rate. The reduction of the proportion of subjects developing frank 'erosive' osteoarthritis in previously stationary OA joints in the CS- and CPS-treated groups is of clinical interest. Our clinical data do not favour the hypothesis that a drop-out of patients with more progressive OA in the treated groups led to a selection of milder cases and a significant retardation of the X-ray changes at 3-year follow-up. None of the patients mentioned a worsening of the clinical condition as a reason for withdrawal from the study, and X-rays were not taken after less than 1 year of follow-up.

It is admitted that fewer interphalangeal joints of the CPS-treated patients, when enrolled in the study, were affected. In addition, these joints scored lower in the anatomical phase score system. Fewer patients of this group had their interphalangeal joints in destructive phases. It is speculative to argue that these patients belonged to a less aggressive population not at risk of developing 'erosive' OA. By no means do proportionally less erosive finger joints at the time of inclusion indicate a lower risk for the CPS-treated patients of developing erosive OA in previously non-erosive OA joints. Otherwise, the development of 'erosive' OA during follow-up might have been expected to occur more

frequently in a population with higher proportions of 'non-erosive' OA patients. The fact that CPS-treated patients reported as many symptoms as the controls when included in the study certainly did not forbode a benign course of the disease. A increased number (although not significant) of new OA joints in the CPS-treated patients compared to the controls (45.9% and 32.6% in the CPS-treated patients and in the Pl-Tot group, respectively) may illustrate this thesis.

Finger joint OA becomes symptomatic during inflammatory episodes associated with the onset of 'erosive' or 'inflammatory' osteoarthritis. The pathogenic mechanisms that initiate the destructive phases in the IP joints of these patients are not known. Chondroitin sulphates seem to interfere with the onset of these destructive phases, and this probably explains the symptom-modifying properties of these drugs [48,49]. Sequential X-rays showed that remodelling only occurred in interphalangeal joints that had progressed through destructive phases, and that remodelling occurred in all eroded finger joints [3]. Remodelled distal and proximal interphalangeal finger joints present the typical nodal appearance of Heberden's and Bouchard's nodules and limit the daily activities of the hands. When interfering with the onset of 'inflammatory' or 'erosive' OA, chondroitin sulphates obviously prevent the formation of nodosities in the finger joints. Possibly, retardation of OA progression is related to the effects of these drugs on the repair function of connective tissue cells, e.g. articular cartilage chondrocytes and synovial lining cells [26–28,30–32,41]. These properties allow us to classify these agents among the 'disease-modifying osteoarthritis drugs' (DMOAD [34,35]).

This report illustrates that finger joint OA is an appropriate model to study the natural evolution of OA in humans and to test the therapeutical efficacy of DMOAD. The data recorded during these pilot studies will help investigators to design future long-term clinical experiments. The information obtained can help to estimate the size of the changes expected in some selected variables in a given patient cohort. This knowledge and the proportion of withdrawals observed may also help to define the numbers of patients to be included in such trials.

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