Quality of life assessment during six months of NSAID treatment [Gonarthrosis and quality of life (GOAL) Study]

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Abstract

Objective

To identify the time point of the greatest degree of improvement in daily living activities, pain and depression in patients with osteoarthritis (OA) of the knee during 6 months of treatment with NSAIDs, in order to define compliance and drop-out rate.

Methods

107 patients were recruited into a multicentre, prospective, randomized, controlled trial comparing two treatments, piroxicam-beta-cyclodextrin (PBCD) and slow release diclofenac (DCL).

Results

The greatest improvement in quality of life occurred in both groups after 3 months, with a slight further gain observed by the end of treatment. The Stanford Health Assessment Questionnaire score improved ($p < 0.05$ vs baseline) at 3 and 6 months with PBCD and at 6 months with DCL. The Arthritis Impact Measurement Scale score improved ($p < 0.05$ vs baseline) after 6 months in both groups. Significant ($p < 0.05$ vs baseline) improvement in other psychological and pain scores were recorded in both groups after 3 and 6 months. Compliance with treatment at 3 months was 73% for PBCD and 72% for DCL, and was 60% in both groups at 6 months.

Conclusions

The results of this study indicate that the optimal length of time for an NSAID trial in OA patients is 3 months, when assessment of daily living activities is considered as the main outcome criterion.

Key words

Gonarthrosis, quality of life, NSAIDs, long-term treatment

Introduction

Osteoarthritis (OA) comprises a group of rheumatic disorders which has been estimated to affect more than 10% of the population over the age of 65 years (1). It is one of the most common causes of consultation with the family physician (2). Signs and symptoms of OA of the knee may be found in more than 12% of adult patients (3). The disease fairly often leads to major disability; 20.4 ‰ patients eventually require arthroplasty as the last resort for OA-related symptoms (4). OA is characterized by a variable inflammatory component and non-steroidal anti-inflammatory drugs (NSAIDs) are often needed to treat the symptoms and improve functioning (5, 6). NSAID-associated toxicity, however, is well known, and it is of crucial importance to be aware of the real benefit of NSAIDs in a patient population at increased risk, such as those with OA of the knee (7, 8). The primary aim of this study was to assess the daily living activities of patients with OA of the knee during a 24-week trial designed to compare two currently used NSAIDs, piroxicam-beta-cyclodextrin (PBCD) and diclofenac (DCL), by means of the Stanford Health Assessment Questionnaire (HAQ) (9), translated into Italian and validated (10), and the Performance and Activities Scale (PAS) already employed in another study on OA of the knee (11). Depression, anxiety and pain were measured by means of the Arthritis Impact Measurement Scale (AIMS) (12), the Visual Analogue Scale (VAS) and the Present Pain Index (PPI) (13, 14).

The second aim of our study was to assess how many patients could be maintained on continuous daily treatment and whether such treatment can be recommended for patients with symptomatic OA.

Materials and methods

Patients

This multi-centre, randomized, controlled trial was conducted in 7 Italian rheumatology centres in conformity with Good Clinical Practice standards and was approved by the local ethics committees. All patients gave their informed consent.

107 patients (77 women and 30 men) suffering from OA of the knee, diagnosed on the basis of the American College of Rheumatology (ACR) criteria for the classification of OA (15) were entered into the study. The main inclusion criteria for recruitment were: age 50 - 75 years; daily pain for at least one month; morning stiffness for more than 30 min; and x-ray evidence of joint space narrowing and osteophytes in at least one knee. The Kellgren's score was recorded for the most painful joint in all patients by an independent radiologist who was unaware of the patient's diagnosis (16).

Patients with positive rheumatoid factor, positive anti-nuclear antibodies (ANA), a history of high uric acid or gout, or with hepatitis C virus (HCV) or hepatitis B virus (HBV) antibodies were excluded from the study. Also excluded were patients who had received intra-articular steroid injections during the 3 months preceding this study. Other exclusion criteria were: clinically significant haematological, renal or hepatic disease; diabetes, congestive heart failure, infection or major surgery during the previous month; evidence of gastrointestinal bleeding or peptic ulcer during the past year; use of antiacid drugs for peptic symptoms during the previous 6 months; and any condition capable of influencing drug absorption. Intra-articular injections were not allowed during the trial.

Trial design

After a 2 week wash-out period, the patients were randomized to treatment with either PBCD 20 mg or slow release DCL 100 mg after dinner. Biochemical, haematological and urinary variables were tested, together with occult blood in the stool at entry, after 10 days, and after the 1st, 3rd and 6th month of treatment. At entry, and again at months 1, 3 and 6, the patients were assessed clinically and were asked to complete the HAQ, AIMS, PAS, VAS and PPI questionnaires.

Adverse events

All adverse events, whether spontaneously reported by the patient or observed by the investigator, were recorded on a diary card, and their severity and possible relationship to the treatment were noted. A classification of the events leading to the discontinuation of treatment, and of events possibly or unlikely to be related to the trial drugs was drawn up.

Statistical analysis

All patients who underwent at least the first assessment (day 10) were entered in the intention-to-treat analysis. The last assessment was considered for efficacy variables as well as for adverse events over time.

The comparability of the 2 treatment groups at baseline was assessed by means of the un-

Table I. Main patient characteristics (mean ± SE) at baseline (ns = not significant).

	PBCD	DCL	p
Age (years)	60.9 ± 1	61.5 ± 1.3	ns
Height (cm)	161.2 ± 0.8	164.5 ± 0.8	< 0.01
Weight (kg)	76.8 ± 1.8	75.5 ± 1.6	ns
Sex			
Male	9	21	< 0.05
Female	43	34	
Total	52	55	
OA duration (mo.)	45.3 ± 5.3	38.1 ± 4.1	ns
Kellgren's score			
Affected knees	2.35 ± 0.07	2.40 ± 0.07	ns
Both knees	2.02 ± 0.09	2.26 ± 0.08	ns
% Grade 2	40	33	
% Grade 3	60	67	

paired t-test for continuous variables and the chi-square test for dichotomous variables.
One-way ANOVA, followed by Dunnett's test, was used to compare the outcomes measured at 3 and 6 months vs baseline values in the within-treatment analysis.

Analysis of covariance, in which the outcomes measured at each observation time were considered as dependent variables, was performed. In this analysis, differences between the groups were examined after adjustment for sex and with the baseline values for the outcome measures as co-variates. The paired t-test was used to analyze the biochemical, haematological and urinary parameters and the chi-square test to compare the incidence of adverse events.

Results

Patients

Fifty-two patients were randomized to treatment with PBCD and 55 to treatment with DCL.
At baseline the 2 treatment groups were well matched for age, weight, duration of OA, and the Kellgren score. They were not well matched for sex distribution (p < 0.05) owing to natural occurrence of the disease, or for height (p < 0.01) (Table I). However, the effect of an unpaired sex distribution on statisti-

cal analyses of the safety of NSAIDs is usually considered to be small (17).
One patient in the PBCD group and two in the DCL group had a positive rheumatoid factor test, but none of them fulfilled the criteria for rheumatoid arthritis and they were therefore included in the study. The duration of symptoms, the grade of OA of the knee, and the haematology, biochemistry, ESR, urine analysis and pain scores were similar for the two groups.

Clinical efficacy (Table II; Fig. 1)

Daily living activities, as assessed by the HAQ, showed a progressive improvement in their scores which was significant (p < 0.05 vs baseline) at month 6 in the DCL group and at months 3 and 6 in the PBCD group (p < 0.05). The PAS scores showed a statistically significant improvement (p < 0.05 vs baseline) at months 3 and 6 in both groups. The 24-week results for the AIMS depression scale also showed a significant improve-
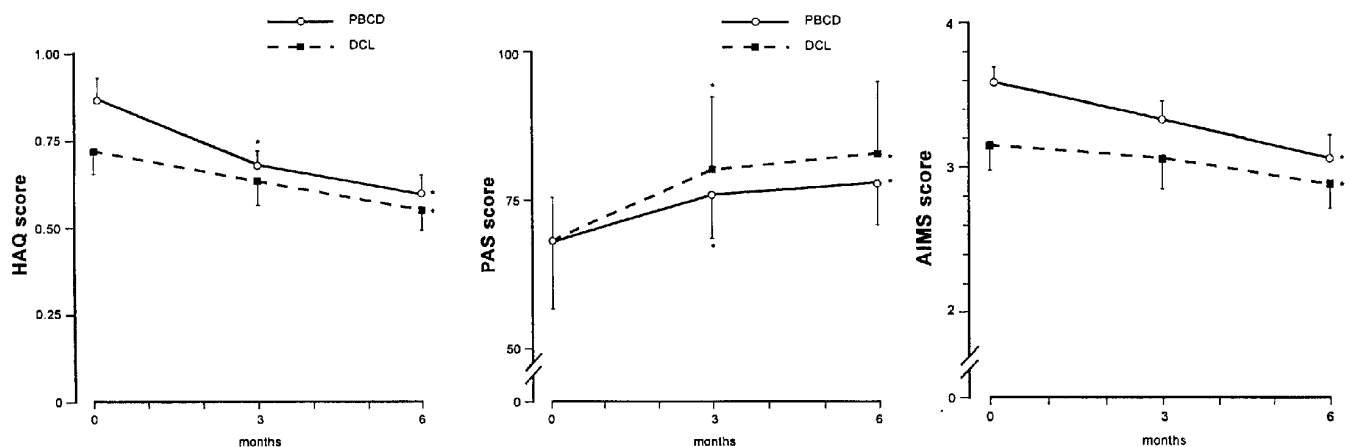

Fig. 1. Changes in the HAQ, PAS and AIMS scores (mean ± SE) *p < 0.05 vs baseline.

Table II. Scores (mean ± SE) of scales and questionnaires at each observation time (*p < 0.05 vs baseline at month 0).

	PBCD□ Month 0	PBCD□ Month 3	PBCD□ Month 6	DCL◆ Month 0	DCL◆ Month 3	DCL◆ Month 6
HAQ	0.89 ± 0.08	0.71 ± 0.06*	0.66 ± 0.06*	0.71 ± 0.06	0.64 ± 0.08	0.57 ± 0.07*
PAS	71.54 ± 2.04	77.12 ± 2.10*	78.85 ± 2.17*	71.27 ± 1.89	79.27 ± 1.97*	81.45 ± 2.02*
PPI	2.33 ± 0.11	1.94 ± 0.12*	1.80 ± 0.13*	2.2 ± 0.10	1.8 ± 0.10*	1.62 ± 0.12*
VAS	53.11 ± 2.72	43.26 ± 3.12*	37.9 ± 3.30*	51.26 ± 2.56	39.92 ± 3.20*	38.34 ± 3.45*
AIMS	3.59 ± 0.15	3.38 ± 0.16	3.08 ± 0.18*	3.18 ± 0.18	3.07 ± 0.20	2.85 ± 0.17*

	□ n = 50	◆ n = 53		□ √n = 51	◆ √n = 55
HAQ: Health Assessment Questionnaire			VAS: Visual Analogue Scale		
PAS: Performances and Activities Scale	n = 52	n = 55	AIMS: Arthritis Impact Measurement Scale	n = 51	n = 55
PPI: Present Pain Index	n = 51	n = 55			

All analyses were made on an intention-to-treat basis; patients with at least the assessment on day 10 were considered eligible for analysis.

Table III. Adverse events in the two treatment groups.

Event	PBCD	DCL
Oral ulcers	1	3
Dry mouth	4	6
Dysgeusia	1	2
Epigastric discomfort	16	19
Gastrointestinal bleeding	1	2
Peptic ulcer	1	-
Nausea	5	4
Diarrhea	3	5
Headache	1	1
Insomnia	1	1
Dizziness	4	2
Tinnitus	1	-
Transaminase elevated	2	1
Pancreatitis	-	1
Proteinuria	1	-
Glycosuria	1	-
Ankle oedema	1	-
Pruritus	3	3
Urticaria	1	1
Total number of adverse events	48	51

	Mild	Moderate	Severe	Mild	Moderate	Severe
	75%	25%	0	69%	27%	4%
Total no. of patients with adverse events (*pts. enrolled)		23 (52*)			28 (55*)	

ment (p < 0.05 vs baseline) in both treatment groups (Fig. 2).

Compared to baseline, the VAS and PPI values decreased (p < 0.05) at months 3 and 6 in both groups, but no significant differences were observed between the 3 and 6 month values in either group.

Table IV. Number of patients still on treatment at the 3rd and 6th months, and reasons for discontinuation among the patients who dropped out.

	PBCD	DCL
Randomized	52	55
Completed 3 mos. of treatment	38	40
Completed 6 mos. of treatment	31	33
Drop-outs due to:		
Lack of efficacy	2	
Adverse events	5	9
Intercurrent illness	2	1
Protocol violation*	4	5
Lost to follow-up**	8	7

*Unpermitted concomitant treatments;
**Could not keep up with the schedule of clinical and laboratory controls.

Adverse events and drug safety
The overall incidence of adverse events, the number of dropouts due to adverse events, concurrent illness or acute relapses, and the number of patients lost to follow-up were similar in the two groups (Tables III to V). After 10 days of treatment, one patient in the PBCD group and 2 in the DCL group presented faecal occult blood test positivity, which disappeared at the subsequent observation times.

Table V. Drop-outs due to adverse events.

Event	PBCD (5/52) Intensity	Causal relation	Event	DCL (9/55) Intensity	Causal relation
Abdominal pain	moderate	possible	Epigastric pain	moderate	probable
Duodenal ulcer	moderate	highly prob.	Epigastric pain	severe	probable
Epigastric pain	mild	possible	Epigastric pain	mild	probable
Insomnia	moderate	unrelated	Epigastric pain	mild	probable
Ankle oedema	mild	probable	Epigastric pain	mild	possible
			Heartburn	moderate	possible
			Abdominal pain	moderate	highly prob.
			Pancreatitis	severe	possible
			Diarrhea	moderate	probable

Analysis of the patients over time revealed that, on the whole, the two study drugs were well tolerated. Haematological, liver function, kidney and urinary parameters remained unchanged at the various time points (Table VI).

Continuation on treatment
There was no significant difference in the number of patients who continued with the treatment over time in the two groups. Two patients in the PBCD group withdrew from the study because of poor efficacy. There were 5 drop-outs in the PBCD group and 9 in the DCL group owing to adverse events, and 2 drop-outs in the PBCD group and 1 in the DCL group due to concurrent illnesses. Eight patients in the PBCD group and 7 in the DCL group were lost to follow-up; they spontaneously withdrew from the study as they were unable to complete the heavy schedule of clinical and laboratory assessments in the first month. Nine patients violated the protocol by taking unpermitted drugs (3 inhaled corticosteroids; 1 oral corticosteroid; 5 shifted to other NSAIDs) (Table IV).

Discussion
Osteoarthritis remains a challenging disease in terms of its physiopathology, the definition of possible subsets and the optimal medical approach. The natural course of this slow, chronic progressive disorder is not well understood (18). Given the hypothesis that OA is a long-lasting "chronic inflammatory" disease, any treatment must last long enough to allow the possible "re-setting" of the inflammatory process (19, 20). We also know that "metabolic" and "mechanical"

Table VI. Laboratory safety parameters (mean ± SE).

	PBCD					DCL					PBCD*	DCL*
	Month 0	Day 10	Month 1	Month 3	Month 6	Month 0	Day 10	Month 1	Month 3	Month 6		
Red blood cells (1 x 10⁶/mm³)	4.72 ± 0.09	4.6 ± 0.08	4.56 ± 0.07	4.57 ± 0.07	4.61 ± 0.08	4.62 ± 0.06	4.55 ± 0.08	4.51 ± 0.06	4.49 ± 0.06	4.5 ± 0.08	0.37	0
Hemoglobin (g/dl)	13.57 ± 0.16	13.41 ± 0.17	13.24 ± 0.18	13.44 ± 0.21	13.5 ± 0.23	13.86 ± 0.18	13.75 ± 0.23	13.64 ± 0.18	13.61 ± 0.21	13.68 ± 0.24	0.51	0.12
Hematocrit (%)	40.76 ± 0.45	40.16 ± 0.49	39.87 ± 0.42	40.22 ± 0.52	40.08 ± 0.63	40.88 ± 0.48	40.92 ± 0.61	40.3 ± 0.51	39.77 ± 0.47	40.85 ± 0.61	0.88	0.26
MCV (μm³)	86.58 ± 1.02	87.04 ± 1.21	86.18 ± 1.12	86.68 ± 1.27	85.6 ± 137	87.48 ± 0.74	88.11 ± 0.88	87.79 ± 0.6	86.67 ± 0.71	88.44 ± 0.77	0.07	0.15
MCH (pg)	28.44 ± 0.41	28.82 ± 0.47	28.52 ± 0.48	28.78 ± 0.49	28.4 ± 0.57	29.27 ± 0.31	29.4 ± 038	29.51 ± 0.32	29.64 ± 0.38	29.59 ± 0.36	0.42	0.04
MCHC (g/dl)	32.77 ± 0.17	32.84 ± 0.18	32.73 ± 0.19	33.07 ± 0.21	32.87 ± 0.47	33.08 ± 0.17	32.77 ± 0.22	33.15 ± 0.25	33.47 ± 0.3	33.21 ± 0.26	0.86	0.31
Platelets (1 x 10⁶/mm³)	252.64 ± 9.1	254.19 ± 9.27	245.98 ± 9.4	247.78 ± 10.7	257.86 ± 12.44	238.21 ± 7.18	247.49 ± 10.1	242.69 ± 8.11	239.5 ± 7.46	244.37 ± 7.98	0.38	0.59
BUN (mg/dl)	32.76 ± 1.92			37.81 ± 2.12	33.93 ± 2.26	29.71 ± 1.53			28.79 1.66	30.14 ± 2.24	0.78	0.28
ESR (mm/h)	17.5 ± 1.62			17.51 ± 2.26	17.23 ± 2.56	14.51 ± 1.34			12.7 1.24	14.1 ± 1.32	0.99	0.61
Total bilirubin (mg/dl)	0.55 ± 0.03			0.57 ± 0.03	0.56 ± 0.04	0.62 ± 0.03			0.64 0.03	0.66 ± 0.03	0.62	0.06
GOT (U/l)	18.71 ± 0.9			19.53 ± 1.15	19.6 ± 1.27	18.4 ± 0.76			21.55 1.31	20.03 ± 1.32	0.19	0.1
GPT (U/l)	23.18 ± 1.67			23.75 ± 2.33	23.03 ± 2.26	23.03 ± 1.71			27.26 2.66	25.41 ± 2.85	0.64	0.22
Gamma-GT (U/l)	19.39 ± 1.55			17.49 ± 0.87	16.67 ± 1.07	20.9 ± 1.4			22.74 1.69	21.79 ± 2.06	032	0.72
Alkaline phosphatase (U/ml)	131.94 ± 7.12			133.17 ± 9.04	137.1 ± 8.84	131.45 ± 7.09			134.11 6.6	132.76 ± 7.01	0.17	0.89
Creatinine (mg/dl)	0.74 ± 0.03			0.78 ± 0.02	0.78 ± 0.03	0.78 ± 0.03			0.76 0.04	0.79 ± 0.03	0.81	0.91

*p value month 0 vs month 6

alterations play a crucial role, since they are capable of priming or amplifying the inflammatory damage (21, 22).

The first point of interest of our study is that the greatest degree of improvement in pain and function was achieved in the first 3 months in both arms. This trend did not emerge in Dieppe's study (6), where clinical assessments were done only every 6 months. Since that time, a 3-month period has been reported as likely to be long enough to obtain the best result (23). The findings of our study, although limited by the absence of a placebo control group, seem to give further support to this hypothesis. Therefore it seems reasonable that the treatment period in future trials with NSAIDs should not exceed 3 months. After this period, any further improvement would appear to be clinically irrelevant in terms both of pain and functional capacity. Certainly, our data do not suggest the degree of improvement previously reported in Ward *et al.*'s study (23) where, however, there was an unexplained discrepancy between the improvement in pain intensity and the improvement in function. Whether the lesser degree of improvement in our study depends on an overly conservative assessment or on the presence of very severe disease in our population cannot be established at the moment.

The second outcome of our study is that we were able to maintain 60% of the patients initially recruited on treatment for 6 months. Drop-outs were due mainly to patients being lost to follow-up and, to a lesser extent, to the occurrence of adverse events or clinical failure. No significant differences were observed between the two arms of the study. We therefore believe that this reflects the general pattern among OA patients, regardless of which drug is administered. This conclusion is in full agreement with recent data in a larger patient sample treated with tiaprofenic acid, indomethacin or placebo (24). Dieppe *et al.* (6) have clearly demonstrated that the first 6 months are crucial for establishing overall survival on treatment. Concerning safety, we observed the expected per-

centage of adverse drug reactions to the two drugs. Only one of the patients had to discontinue the medication because of gastro-intestinal bleeding. In the population as a whole, discontinuation was mainly due to gastrointestinal disorders, as may be expected when using NSAIDs (7, 8).

In conclusion, PBCD and DCL were able to improve daily living activities in patients with OA of the knee; this improvement occurred mainly in the course of the first 3 months of treatment. The overall rate of continuation on treatment was 73% and 60% at 3 and 6 months respectively. The most suitable length of time for future trials with NSAIDs in OA, when daily living activity is the main outcome criterion, should be 3 months.

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