EXTENDED REPORT

A prospective randomised multicentre study comparing continuous and intermittent treatment with celecoxib in patients with osteoarthritis of the knee or hip

F P Luyten, P Geusens, M Malaise, L De Clerck, R Westhovens, F Raeman, D Vander Mijnsbrugge, L Mathy, J P Hauzeur, F De Keyser, F Van den Bosch

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Correspondence to: Professor F P Luyten, Department of Rheumatology, University Hospitals KULeuven, Herestraat 49, B3000 Leuven, Belgium; frank.luyten@uz.kuleuven.ac.be

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Objective: To compare the effects of continuous and intermittent celecoxib treatment in patients with knee or hip osteoarthritis in flare.
Methods: In this 24-week, prospective, randomised, double-blind, placebo-controlled study, patients were randomly assigned to receive continuous (n = 62) or intermittent (n = 61) treatment with celecoxib 200 mg once daily. The primary efficacy end point was the area under the curve (AUC) of the change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total scores between baseline and week 24 divided by the time interval. Secondary end points included the percentage of days with intake of the flare drug, the AUC of the change in the WOMAC total scores, the mean change from baseline in the WOMAC scores, and the patient's and physician's global assessment of osteoarthritis.
Results: There were no significant differences between patients randomised to continuous or intermittent treatment in the primary end point or most of the secondary end points, although a consistent trend supporting continuous treatment was observed. The percentage of days with intake of the flare drug was significantly lower (p = 0.031) in the group receiving continuous versus intermittent celecoxib. Both treatment regimens were well tolerated.
Conclusion: The results of this pilot study indicate a potential clinical difference between continuous and intermittent treatment with celecoxib, and may be useful in designing future trials. A larger trial on both efficacy and safety outcomes is required for conclusive evidence in favour of either continuous or intermittent treatment.

Evidence for structure-modifying pharmacological agents that directly interfere with the progression of osteoarthritis is currently insufficient.[1–4] The goal of treatment in patients with osteoarthritis is still primarily to reduce the signs and symptoms of the disease while maintaining quality of life and functional independence.

Prostaglandins most probably have an important role in the pathophysiology of osteoarthritis. Stimulation of articular chrondrocytes by proinflammatory cytokines increases prostaglandin E_2 synthesis, which coincides with the up regulation in expression of cyclo-oxygenase (COX)2 but not of COX1.[5–8] Raised production of prostaglandin E_2 and COX2 has been implicated in cartilage matrix destruction.[9 10] Therefore, COX2 may have a pivotal role in progression of osteoarthritis, and its inhibition could potentially limit cartilage damage as well as treat the signs and symptoms. However, the potential advantages of using anti-inflammatory drugs in patients with osteoarthritis need to be balanced against the risk of adverse events, particularly cardiovascular thrombotic events.[11–14]

Numerous controlled clinical studies have proved the efficacy and safety of treatment with the COX2-selective inhibitor, celecoxib, in controlling the signs and symptoms of osteoarthritis.[15–22] To date, no study has investigated the comparative efficacy of every-day, fixed-dose COX2-selective inhibitor therapy (continuous treatment) versus a strategy of taking the same drug on demand (intermittent treatment) in patients with osteoarthritis. Compared with intermittent treatment, continuous treatment may, to some extent, control the disease process better, potentially slowing disease progression. Alternatively, intermittent treatment may effectively reduce the signs and symptoms of osteoarthritis without causing the adverse events that may be associated with continuous treatment.

To investigate the feasibility of prospective clinical trials evaluating intermittent and continuous use of anti-inflammatory or analgesic drugs, we conducted a pilot, randomised study to compare the effects of continuous and intermittent celecoxib treatment over 6 months on the signs and symptoms of osteoarthritis in patients with knee or hip osteoarthritis in flare.

METHODS

Patients

Patients were aged ⩾40 years, with a diagnosis of osteoarthritis of the knee or hip according to American College of Rheumatology criteria,[23 24] and needed frequent anti-inflammatory treatment for their condition (physician's judgement based on the patient's clinical history). Patients were included in the study if they had osteoarthritis in a flare state at the baseline visit, a Functional Capacity Classification of I–III according to Steinbrocker's criteria[25] at screening, and were poor responders to paracetamol (acetaminophen; physician's judgement based on the patient's clinical history).

Abbreviations: AUC, area under the curve; COX, cyclo-oxygenase; NSAID, non-steroidal anti-inflammatory drug; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

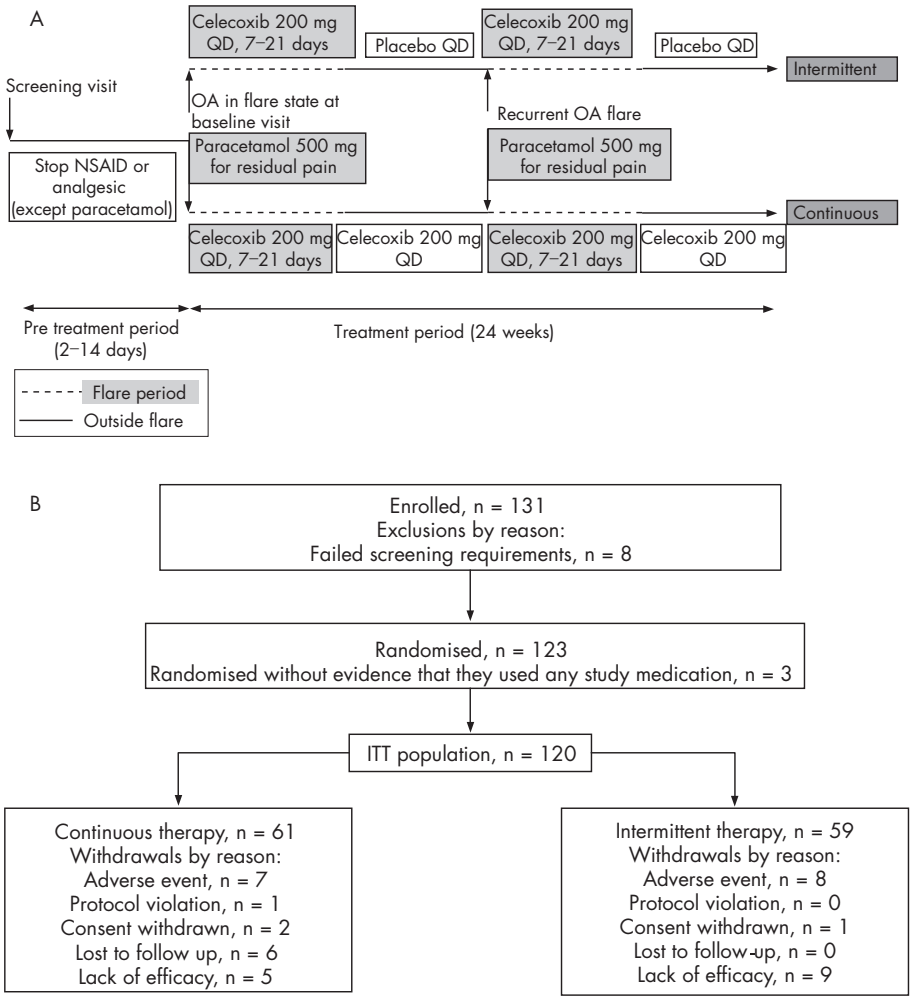

Figure 1 (A) Schematic representation of trial design. (B) Patient disposition. ITT, intent-to-treat; NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; QD, once daily.

For patients receiving analgesic treatment for osteoarthritis at screening, an osteoarthritis flare was recorded if the patient's and physician's global assessment of osteoarthritis was fair, poor or very poor at the baseline visit, and a comparison of the screening and baseline assessments met at least three of the following criteria: a baseline visual analogue scale (VAS) score of at least 40 mm in the patient's assessment of osteoarthritis pain intensity, an increase of $\geqslant$2 points in the Osteoarthritis Severity Index, or an increase of $\geqslant$1 grade in the patient's or the physician's global assessment of arthritis. For patients who were not receiving any treatment for their osteoarthritis and whose osteoarthritis was not controlled at screening, an osteoarthritis flare was recorded if they met at least three of the following criteria during the baseline assessments: a patient's assessment of osteoarthritis pain intensity measurement of at least 40 mm on the VAS, an Osteoarthritis Severity Index of $\geqslant$7, or a patient's or physician's global assessment of arthritis of poor or very poor.

Patients were excluded from the study if they had inflammatory arthritis, gout, acute joint trauma, an anticipated need for any surgical or other invasive procedure during the course of the study, an oesophageal or gastroduodenal ulcer within the 30 days before randomisation, active gastrointestinal disease, severe renal or hepatic disease, a major bleeding disorder, severe cardiac insufficiency, an anticipated need for anti-inflammatory drugs other than the study drug, or known hypersensitivity to COX2-selective inhibitors, salicylates, sulphonamides or non-selective non-steroidal anti-inflammatory drugs (NSAIDs). Patients who were taking aspirin at doses $\leqslant$325 mg/day for at least 30 days before the first dose of the study drug continued their aspirin regimen.

The study was carried out according to the Declaration of Helsinki and Good Clinical Practices guidelines. The study protocol was approved by local institutional review boards/independent ethics committees. All patients gave written informed consent.

Study design

This was a 24-week, prospective, randomised, multicentre, double-blind, placebo-controlled, parallel-group study to compare the effects of continuous and intermittent treatment with celecoxib on the signs and symptoms of knee or hip osteoarthritis in flare. Figure 1A is a schematic representation of the study design.

At screening, patients discontinued any analgesic they were taking for osteoarthritis for 2–14 days, during which time paracetamol at a maximum dose of 3 g/day was permitted. The rescue drug was discontinued 8 h before baseline assessments. The patients' medical history was taken, and physical examination, clinical laboratory tests and osteoarthritis assessments

Table 1 Patient demographics and baseline characteristics

	Celecoxib 200 mg once daily		
	Continuous treatment n = 61	Intermittent treatment n = 59	p Value
Age in years, mean (SD)	64.6 (9.9)	64.9 (10.6)	0.849*
Weight in kg, mean (SD)	75.9 (11.9)	78.3 (15.7)	0.674†
Sex, n (%)			1.000‡
Male	12 (20)	12 (20)	
Female	49 (80)	47 (80)	
Functional Capacity Classification, n (%)			0.452†
Class I	0 (0)	3 (5)	
Class II	37 (61)	35 (59)	
Class III	24 (39)	21 (36)	
Pain, by VAS, 1–10 cm, mean (SD)	7.05 (1.65)	6.82 (1.60)	0.346†
Osteoarthritis Severity Index Score, 0–24, mean (SD)	14.03 (2.84)	13.88 (2.94)	0.769†
Index joint, n (%)			0.481‡
Knee	48 (79)	50 (85)	
Hip	13 (21)	9 (15)	
Previous (within 30 days before inclusion) NSAID use, n (%)	35 (57)	33 (56)	
Previous (within 30 days before inclusion) paracetamol use, n (%)			

NSAID, non-steroidal anti-inflammatory drug; VAS, visual analogue scale.
*t test.
† Mann Whitney U test.
‡ Fisher's test.

were performed at the screening, including the patient's assessment of pain intensity (VAS; 0 mm, no pain; 100 mm, severe pain), the patient's and physician's global assessment of osteoarthritis (5-point scale: 1, very good; 5, very poor) and the Osteoarthritis Severity Index (sum of the scores (0–24) of patient responses to seven inquiries related to osteoarthritis pain, walking distance and activities of daily living; a lower score indicates a better condition).[26]

At baseline, patients meeting the flare criteria underwent the same tests performed at screening and were scored on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Patients responded, by means of a VAS, to 24 component items (a lower WOMAC score indicated a better condition).

Patients were randomised at baseline to either continuous or intermittent celecoxib treatment using a computer-generated randomisation schedule. All patients received celecoxib 200 mg once daily for at least seven consecutive days at the start of the study and discontinued it on resolution of osteoarthritis flare symptoms or after a maximum of 21 days. Thereafter, in the absence of flare, patients randomised to continuous treatment took celecoxib 200 mg once daily for 24 weeks, whereas patients randomised to intermittent treatment took matching placebo. In the intermittent treatment arm, celecoxib use was restricted to only periods of flare. This was achieved by clearly labelling the study drug as ''reserved for the treatment of an osteoarthritis flare'', or ''medication to be taken outside of the flare period''. By contrast with the definition of flare at baseline, which was a physician's assessment based on well-defined criteria, the definition of flare during the treatment period was patients' perception of their symptoms and signs, as mentioned in the written consent.

All osteoarthritis assessments including the WOMAC Index were performed at each study visit (weeks 2, 6, 12, 18 and 24 ($\pm$3 days), or early termination). The patient's global assessment of osteoarthritis was always conducted before intake of the flare drug. In both treatment arms, paracetamol could be used as rescue drug during a flare at any time during the study, except at least 8 h before osteoarthritis evaluations.

Study end points

The primary efficacy end point was the area under the curve (AUC) of the change in the WOMAC total score between baseline and week 24 (value at baseline minus the value at the week 24 visit) divided by the time interval.

Secondary end points included the percentage of days with intake of the flare drug, the AUC of the change in the WOMAC total scores between baseline and weeks 2, 6, 12 and 18, and the last assessment divided by the time interval (the last assessment was defined as the last observation available for a variable), the WOMAC total scores and subscores between baseline and weeks 2, 6, 12, 18 and 24, and the last assessment, the patient's and physician's global assessment of osteoarthritis at weeks 2, 6, 12, 18 and 24, and the last assessment, the number of paracetamol tablets (rescue drug) taken per day, and the number and percentage of patients discontinuing the study drug over time for treatment failure. The incidence of the primary end point in the two treatment arms was further assessed in retrospective analyses according to three stratified groups: previous NSAID use, osteoarthritis of the knee or hip, and the functional capacity class. The percentage of days with intake of the flare drug was defined as the proportion of total days in the treatment period that the patients judged themselves to be in flare and hence took the flare drug (celecoxib 200 mg once daily).

The investigators documented all adverse events (serious and non-serious) directly observed or reported by the patient.

Statistical analyses

As this was a pilot study, and there have been no previous investigations, a formal sample-size calculation was not performed. On the basis of the recruitment capacity of participating centres and a maximum recruitment period of 6 months, the total number of patients to be included was fixed at 150. A total of 100 evaluable patients was aimed for (50 per treatment arm), considering a drop-out rate of approximately 30%.

The homogeneity of the treatment groups at inclusion was tested using a one-way analysis of variance for quantitative parameters and a χ^2 test for qualitative parameters. All

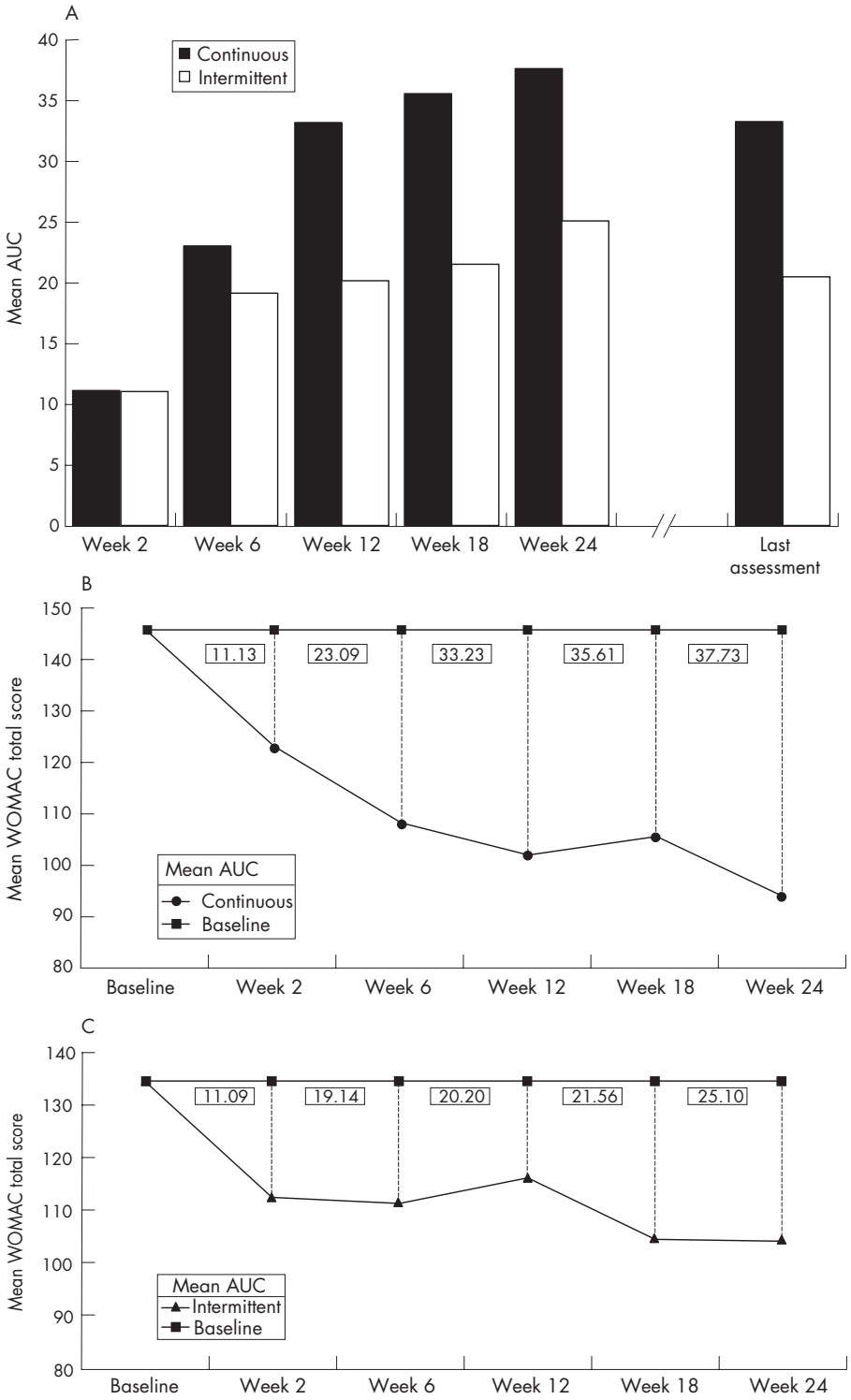

Figure 2 (A) Mean area under the curve (AUC) between baseline and week 2, 6, 12, 18 and 24, and the last assessment of the change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total scores, divided by the number of days between baseline and week 2, 6, 12, 18 and 24, and the last assessment, respectively. The primary efficacy end point was the mean AUC of the change in WOMAC total scores between baseline and week 24, divided by the number of days between baseline and week 24. A positive AUC value corresponds to a decrease in the WOMAC total scores, which indicates an improvement in condition. (B) AUC for the continuous treatment arm. (C) AUC for the intermittent treatment arm.

statistical tests were performed two sided at the 5% level of significance. The intent-to-treat population (all randomised patients who took at least one dose of study drug) was considered in the analyses.

The last-observation-carried-forward approach was used for missing data or data obtained on days outside the observation window. Mean changes in the WOMAC total scores over the 6-month treatment period were analysed using a two-way

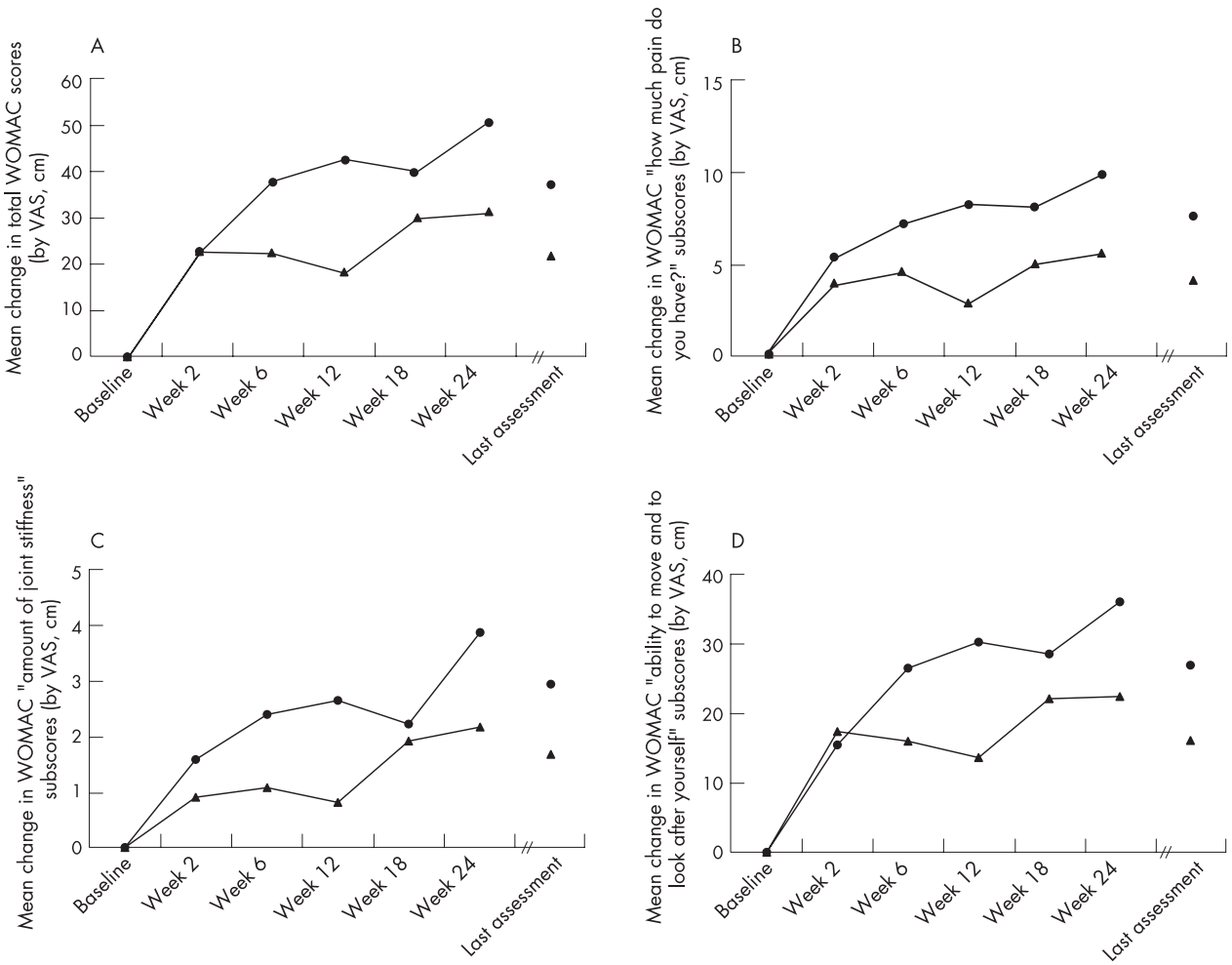

Figure 3 (A) Mean change from baseline in the total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores. Mean change from baseline in the subscore categories (B) ''how much pain do you have'', (C) ''amount of joint stiffness'' and (D) ''ability to move and to look after yourself''. A greater change in the WOMAC scores indicates greater improvement in condition. Filled circles, continuous treatment group; filled triangles, intermittent treatment group. VAS, visual analogue scale.

analysis of covariance, with treatment and centre as the main factors and baseline value as the covariate. The percentage of days with intake of the flare drug was calculated on the basis of the tablet count and was analysed using the Mann–Whitney U test. The number of flare drug tablets taken in the two groups was analysed by a two-group t test. In the retrospective analyses, the comparison between the two arms for the primary end point was performed using analysis of covariance, with treatment as the main factor.

RESULTS

Patients

Patients (n = 131) were enrolled in 18 centres between June 2002 and April 2003. Of these, eight were not randomised as they failed the screening requirements, and three were randomised but there was no evidence that they used any study drug. The remaining 120 patients constituted the intent-to-treat population (fig 1B). Of these, 21 and 18 patients in the continuous and intermittent treatment groups, respectively, discontinued the study prematurely. The most common reasons for discontinuation were adverse events (n = 15) and lack of efficacy (n = 14; fig 1B). The mean age of patients across treatment groups was 65 years and most patients were women. We found no significant differences in the baseline characteristics or medical history between the treatment groups (table 1).

Primary end point

The mean (standard deviation (SD)) change in the WOMAC total score between baseline and week 24 as measured by the AUC was 37.7 (40.00) in the continuous and 25.10 (32.01) in the intermittent treatment group (fig 2A–C). We found a numerical, but not significant, difference between the two treatment groups (95% confidence interval (CI) for the continuous treatment group 24.76 to 50.70, and that for the intermittent treatment group 14.86 to 35.34).

Secondary end points

The mean (SD) percentage of days with intake of the flare drug was significantly lower (p = 0.031) in the continuous than in the intermittent treatment group (47.85 (20.70) and 52.79 (14.33), respectively).

The mean change in the WOMAC total scores as measured by AUC increased numerically, but not significantly, from week 2 to week 18 for both treatment groups (fig 2A–C). We found no significant differences between continuous or intermittent treatment groups in the total WOMAC scores or any of the

Table 2 Patient's and physician's global assessment of osteoarthritis after treatment with celecoxib 200 mg once daily—''very good'' and ''good'' ratings

	Patient's assessment* (%)				Physician's assessment* (%)			
	Continuous treatment		Intermittent treatment		Continuous treatment		Intermittent treatment	
	Very good	Good	Very good	Good	Very good	Good	Very good	Good
Baseline	0	0	0	0	0	0	0	0
Week 2	0	31	0	27	0	27	0	31
Week 6	4	40	0	33	2	47	0	35
Week 12	4	46	2	26	6	46	0	28
Week 18	9	36	5	30	9	36	3	43
Week 24	12	41	5	32	12	46	0	44
Last assessment	10	33	3	27	10	36	0	32

*p>0.05 between the two treatment groups at all time points.

subscores. However, there was a general trend towards greater mean changes in the WOMAC total scores from baseline in the continuous treatment group than in the intermittent treatment group at all time points (fig 3A). Similar trends were observed for all three subscores (fig 3B–D). The greatest mean changes occurred in the category ''ability to move around and to look after yourself'' (fig 3D).

A higher percentage of patients from the continuous treatment group rated their osteoarthritis as very good or good than those in the intermittent treatment group at all time points (table 2). More doctors rated osteoarthritis as very good at all time points for those patients receiving continuous treatment compared with those receiving intermittent treatment (table 2). However, these trends were not supported by a significant difference between the treatment groups ($p = 0$).

Patients receiving intermittent treatment took more rescue drug daily (mean number of tablets 0.68 (SD 0.56)) than those receiving continuous treatment (mean 0.50 (SD 0.47)). Also, more patients (15%) from the intermittent treatment group discontinued the study drug early because of treatment failure than patients from the continuous treatment group (8%). Again, the differences between the two groups were not statistically significant for either measure.

Retrospective analyses

We found a significant difference in the incidence of the primary efficacy variable between the two treatment arms for patients who had not used NSAIDs previously ($p = 0.03$), but not in those who had a record of previous NSAID use (table 3). We also found no significant difference between the two treatment arms for the joint involved or the functional capacity class.

Safety

Both treatment regimens were well tolerated, with similar rates of withdrawal due to adverse events (additional data are available online at http://ard.bmjjournals.com/supplemental). Most adverse events were mild or moderate in severity. Cardiac failure was reported in 1 (2%) patient from the continuous treatment group, but the study drug was not considered to be the cause. Hypertension was observed in two patients overall, 1 (2%) from each treatment group, and this was believed to be related to the study treatment in both cases. Aggravated hypertension was observed in 1 (2%) patient from the intermittent treatment group and was not related to the study treatment.

DISCUSSION

Our results support the findings from a recently published randomised controlled trial that treatment with celecoxib is effective in managing the signs and symptoms of osteoarthritis (regardless of whether the dose is part of a continuous or intermittent regimen).[27] To our knowledge, this is the first prospective study to directly compare the effects of continuous versus intermittent treatment with a COX2-selective inhibitor in patients with osteoarthritis.

Except for the percentage of days with intake of the flare drug, we found no significant differences between the

Table 3 Retrospective analyses: incidence of the primary end point according to location of osteoarthritis, Functional Capacity Class and previous use of non-steroidal anti-inflammatory drugs, after treatment with celecoxib 200 mg once daily

	AUC of the change in WOMAC total score between baseline and week 24, divided by the number of days between baseline and week 24		
	Continuous treatment*	Intermittent treatment*	p Value†
Previous NSAID use			
No	47.85 (34.49; 16)	26.46 (27.42; 19)	0.030
Yes	30.69 (42.74; 23)	23.88 (36.31; 21)	0.560
Location of osteoarthritis			
Knee	33.58 (41.21; 28)	25.86 (31.87; 33)	0.422
Hip	39.47 (28.01; 11)	35.21 (36.01; 7)	0.230
Functional capacity class			
Class I/II	36.39 (47.89; 22)	17.63 (27.13; 23)	0.153
Class III	75.92 (11.90; 17)	75.92 (11.90; 17)	0.603

AUC, area under the curve; NSAID, non-steroidal anti-inflammatory drug; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
*Values are mean (SD; n).
†p value with treatment as factor.

continuous and intermittent regimens. However, a consistent trend supporting a beneficial effect of continuous treatment was observed for most of the end points. Pain and function were improved by similar levels, regardless of whether patients received a continuous or intermittent treatment with celecoxib, as reflected by the mean change in WOMAC total score between baseline and week 24. There was also a consistent tendency for more improvement in patients receiving continuous treatment, as evidenced by greater changes in WOMAC scores, a reduced requirement for the flare drug, and improvements in patient's and physician's assessment of osteoarthritis.

This was a pilot study with a relatively small patient population, which limited the capacity to detect clinically relevant differences between treatment groups. On the basis of these results, an example for power calculation would be that 406 patients would be required to detect a medically relevant and achievable difference of 0.197 times the SD in the primary end point (equivalent to a difference of three flares) between both treatment arms. However, another way of reviewing the results of this study could be to opt for future studies on patient preference for either a continuous or an intermittent regimen. A crossover design would be needed for this purpose. Additionally, differences in patient characteristics may also have contributed to the lack of statistically significant differences in our study, some of which were investigated in retrospective analyses. Surprisingly, our results show that continuous treatment was more beneficial than intermittent treatment in patients without a record of previous NSAID use, but not in those who had used NSAIDs before. The relevance of these results remains to be elucidated.

An advantage of continuous treatment over intermittent treatment could be that continuous treatment provides better drug coverage and may be more effective in slowing disease progression. However, data available currently are insufficient to support this statement. Structural data from large prospective trials such as the Glucosamine/Chondroitin Arthritis Intervention Trial[27] will further tackle this question.

Conversely, intermittent treatment may be associated with fewer adverse events compared with continuous treatment, although this was not observed in our study. Both treatment regimens were well tolerated and there was no marked difference in the number or severity of adverse events between groups.

The cardiovascular safety of non-selective NSAIDs and COX2-selective inhibitors has recently become a prominent issue. As continuous treatment with a non-selective NSAID or COX2-selective inhibitor could increase the risk for cardiovascular events in the long term, the potential for harm must be carefully weighed against the benefits. The incidence of cardiovascular events was very low in both treatment groups in our study (additional data available online at http://ard.bmjjournals.com/supplemental). However, the treatment period was short (6 months) compared with previous long-term studies that reported cardiovascular adverse events, which were also dose dependent.[11 12]

Given the small size of this study, it is difficult to draw definitive conclusions about the relative benefits of continuous or intermittent treatment with celecoxib. Current recommendations from regulatory agencies are to treat patients with arthritis using non-selective NSAIDs and COX2-selective inhibitors at the lowest dose for the shortest possible duration. Therefore, as data available are yet insufficient to support either a continuous or an intermittent regimen, we believe that intermittent treatment could be tried first, failing which, continuous treatment could be initiated. For many patients, intermittent treatment with rescue drug may be more feasible than continuous treatment. Further investigations with respect to patient preference and disease progression are required. Importantly, this study provides useful information for the design of future studies.

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Authors' affiliations

F P Luyten, R Westhovens, Department of Rheumatology, University Hospitals KULeuven, Leuven, Belgium
P Geusens, Biomedical Research Center, University Hasselt, Campus Diepenbeek, Belgium
M Malaise, L Mathy, J P Hauzeur, Department of Rheumatology, University Hospital Liège, Liège, Belgium
L De Clerck, Department of Rheumatology, University Hospital Antwerp, Antwerp, Belgium
F Raeman, Department of Rheumatology, Jan Palfijn Hospital, ZNA, Merksem, Antwerp, Belgium
D Vander Mijnsbrugge, Pfizer Inc, Belgium
F De Keyser, F Van den Bosch, Department of Rheumatology, Elisabeth Hospital Sijsele-Damme, Sijsele-Damme, Belgium

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