Ankylosing spondylitis: what is the optimum duration of a clinical study? A one year versus a 6 weeks non-steroidal anti-inflammatory drug trial

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Abstract

Objective. To consider the relevance of the duration of a clinical trial in ankylosing spondylitis: long-term (i.e. 1 yr) *vs* short-term (i.e. 6 weeks) assessment of a non-steroidal anti-inflammatory drug (NSAID)–placebo controlled study.

Methods. The design was a prospective, multicentre, double-blind, placebo-controlled study of 6 weeks duration with a 12 months double-blind extension. Study drugs were placebo ($n = 121$) or active NSAID ($n = 352$). A decrease of at least 50% in pain and/or global assessment and/or functional impairment during the study defined the response to treatment. The percentage of patients discontinuing the study drug over time (life table analysis) permitted the evaluation of both the efficacy and toxicity.

Results. Among the 473 recruited patients, the percentage of responders was similar at 1 yr and week 6 with a highly statistically significant difference in favour of the active NSAID groups when compared to placebo (at 1 yr, 17% in the placebo group *vs* 37, 50 and 43% in the piroxicam 20 mg, meloxicam 15 mg and meloxicam 22.5 mg, respectively, for the patient's overall assessment) without any statistically significant difference between the three active groups. However, evaluation of the patients discontinuing the study drug during the 1 yr of the study permitted the detection of a statistically significant difference between the active NSAID groups. A lower percentage of patients taking meloxicam 22.5 mg had to discontinue the study drug when compared to either meloxicam 15 mg or piroxicam 20 mg (37% *vs* 53% and 53%, respectively, $P < 0.05$). By 52 weeks, drug-related upper gastrointestinal adverse events occurred in 13, 32, 20 and 18% in the placebo, piroxicam 20 mg, meloxicam 15 mg and meloxicam 22.5 mg groups, respectively. Some of the adverse events occurred only after week 6.

Conclusion. This study suggests that a 1 yr trial might be of optimum value compared to a 6 week assessment in order to define better the efficacy and tolerability of NSAIDs in ankylosing spondylitis.

KEY WORDS: Ankylosing spondylitis, NSAIDs, Clinical trial, Meloxicam, Piroxicam, Placebo.

Axial involvement of ankylosing spondylitis is responsible for inflammatory pain, poor posture and, at a late stage, ankylosis [1]. Non-steroidal anti-inflammatory drugs (NSAIDs) are considered the cornerstone of drug

therapy for such axial involvement [2, 3]. Numerous studies have been conducted with NSAIDs, most revealing a rapid effect. Most of these studies are active-controlled studies [4–10] and few of them are placebo-controlled studies [11–14]. Most of the active-controlled studies conclude a non-significant difference between the studied drugs. At variance, the few placebo-controlled trials permit the adequate evaluation of the NSAID treatment effect. The usual short-term duration, i.e. a

few weeks, of these trials does not permit the sustained efficacy profile and the tolerability of these agents in this chronic disabling disease to be well documented [15, 16].

These issues prompted us to conduct a placebo-controlled study comparing the information obtained in the long term (i.e. 1 yr) *vs* the short term (i.e. 6 weeks) concerning the efficacy and tolerability of two active NSAIDs (one of which has previously demonstrated its efficacy in short-term placebo-controlled trial, i.e. piroxicam, and the other, i.e. meloxicam, which has demonstrated a clinically acceptable efficacy/safety profile at a dose of 15 mg/day in rheumatoid arthritis [17–20].

Patients and methods

Patient population

Out-patients fulfilling the modified New York criteria for ankylosing spondylitis were recruited [21]. Other defined criteria for inclusion were: (a) daily NSAID intake during the month preceding the selection visit; (b) a wash-out period of NSAID of 2–15 days before the baseline visit; (c) a flare of the disease at baseline defined by both pain evaluated on a 100 mm length visual analogue scale (VAS) over 40 mm and an increase in pain of at least 30% between the screening and the baseline visits.

Patients with peripheral articular disease, defined by the presence at the screening visit of an active (painful or swollen) peripheral arthritis (excluding hip and shoulder), and those with active inflammatory bowel disease, were excluded as were those with severe concomitant medical illness. Patients who had received corticosteroids during the previous month and/or any slow-acting drug initiated or with an altered dose during the previous 6 months were excluded.

Study design

The double-blind, placebo-controlled, dose-ranging study of 1 yr duration was approved by the ethical review board of each participating centre. The trial was conducted in different centres in four countries (Belgium, France, Germany and the UK).

Study drugs

After confirming that the patient fulfilled the eligibility criteria defined above, patients were randomly assigned to receive placebo, piroxicam 20 mg daily, meloxicam 15 mg daily or meloxicam 22.5 mg daily. Patients received two indistinguishable capsules each evening with a glass of water after food. Those in the placebo group received two capsules of placebo, those in the piroxicam 20 mg group one capsule of piroxicam 20 mg and one of placebo, those in the meloxicam 15 mg group one capsule of placebo and one of meloxicam 15 mg, while those in the 22.5 mg group received one capsule of meloxicam 7.5 mg and one of meloxicam 15 mg. The patients were asked to take the study drugs every day during 1 yr whatever the level of symptoms. Compliance was evaluated by pill count at each visit.

Paracetamol (500 mg per tablet) was used as analgesic rescue during the study.

Assessment criteria

Clinical assessment was made at baseline and after 1, 3, 6, 13, 26, 39 and 52 weeks of therapy by the same investigator. The main evaluations were: (a) patient's overall assessment of disease activity using a 100 mm VAS; (b) pain over the previous 2 days using a 100 mm VAS; (c) functional disability using the Ankylosing Spondylitis Functional Index (ASFI) [22]; (d) degree of inflammation assessed by the latent period before resolution of early morning stiffness (in minutes) and the presence of sleep disturbances due to pain. Sleep impairment was measured using a four-grade scale in which 1 = not bothered, no pain at all; 2 = bothered a little, pain is present part of the time, but mild in character; 3 = bothered a lot, steady or intermittent pain, which usually interferes with sleep; 4 = bothered terribly, the night pain is constant, causes marked interference with sleep and the patient is quite miserable (in this paper, sleep disturbance is considered when the recorded value was at least three); (e) range of motion assessed by the Schober test and the chest expansion in centimetres.

At each visit, the investigators checked for treatment compliance and tolerability. Moreover, at entry, and at weeks 6, 26 and 52 of the study, blood samples were collected to evaluate haematological, liver and renal functions together with C-reactive protein (CRP) determination.

Sample size

The sample size was calculated in order to demonstrate a statistically significant difference between an active NSAID and the placebo during the first 6 weeks of the trial. The changes in the ASFI, in pain and in overall assessment of disease activity during the trial were chosen as the main assessment criteria prior to the study. For the variable ASFI, in a previous reported study, the s.D. was estimated as 5.85 [23]. The clinically relevant treatment difference was determined as three. It was calculated that 103 patients per treatment group would demonstrate this difference when comparing each active group to placebo with an overall α level of 0.05 (leading to $\alpha' = 0.0167$ for multiple treatment comparisons) and a power of at least 0.90 (two tailed). The sample size calculation based on the expected changes in overall disease activity assessment and pain gave similar results or even lower figures (data not shown).

Statistical analysis

The statistical analysis was conducted in order to evaluate both the efficacy and the safety of the different drugs, and also to assess the value of a 1 yr duration trial *vs* a 6 weeks trial. In terms of efficacy, the main outcome measures were as follows.

(a) Responders were defined as subjects in whom the relevant variable decreased by at least 50% during the study period and who did not have to discontinue

the drug because of lack of efficacy during the study period. The variables included global assessment by the patient (VAS), pain (VAS) and functional disability (ASFI). Based on previous experience, we anticipated a 20% placebo effect and a 50% active drug effect after 6 weeks of therapy [4, 11].
(b) The mean changes in all the studied variables during the study period.
(c) The time during which the patient stayed on study drug, without discontinuing it because of either lack of efficacy, toxicity or any reason.

Outcome measures were evaluated on all patients entering the study (intention-to-treat analysis; ITT) and also on those who continued treatment until the end of the study (completer analysis). In order to perform the ITT analysis, the LOCF (Last Observation Carried Forward) technique was used.

The analyses were performed both after 6 weeks and after 1 yr of follow-up.

The statistical analysis used the following methods.

1. Baseline characteristics of the patients were compared using a χ^2 test for nominal variables and a one-way analysis of variance for continuous variables.
2. The percentage of responders in each group was compared using Fisher's exact test.
3. The mean changes in the continuous variables during the study were compared by treatment groups using analysis of variance.
4. Life table analyses (in which the event was defined as the discontinuation of the study drug) were performed. The four studied groups were evaluated using the Kaplan–Meier technique and compared using the log rank test.

In order to evaluate each study drug (piroxicam and meloxicam), a P value of <0.0167 was considered as statistically significant (two tailed) for primary end points (adjustment for multiple treatment comparisons). No adjustment was performed for secondary end points.

The second step consisted of the evaluation of the discrepancies in the results obtained at week 6 and at 1 yr. For this purpose, we calculated and analysed the responder variables observed at week 6 and at 12 months. For the continuous variables, the kappa intraclass coefficient of correlation was used as an index of agreement between the mean changes observed at week 6 and 1 yr [24,25]. Specifically, a value >0.75 is usually considered as excellent agreement and a value <0.40 as poor agreement.

Finally, we determined the value of a long-term systematic intake of NSAIDs by evaluating the efficacy of the study drug between week 6 and week 52. For this, the outcome was the percentage of patients who did not have to discontinue the study drug because of inefficacy between week 6 and week 52.

Results

Patients and study course
Of the 605 screened patients, 473 were included in the trial (see Fig. 1). The most frequent reason for non-

inclusion was the absence of an increase of at least 30% of pain level between screening and baseline visit and/or of <40 mm on pain (VAS) at baseline (56 patients).

Table 1 summarizes patients' characteristics at the start of the trial. There was no statistically significant difference in demographic data or clinical variables among the four groups, except for age, with a clinically irrelevant lower mean age in the placebo group. Figure 1 summarizes the study course. The main reasons for discontinuation of the study drug were lack of efficacy and adverse events. At week 6, 35 patients withdrew (13, 6, 10 and 6 in the placebo, piroxicam 20 mg, meloxicam 15 mg and meloxicam 22.5 mg groups, respectively).

Therefore, 473 patients were included in the 6 week and 1 yr ITT analysis and only 363 and 218 in the 6 week and 1 yr completer analysis, respectively. Both analyses (ITT and completer) showed similar results in the 6 week analysis. By contrast, in the placebo group, because of the high number of drop-outs, the results diverged at 1 yr between the two analyses. Herein, we present the ITT analyses.

Assessment of efficacy
Short-term (6 weeks) efficacy. The first step of the analysis was to check our methodology by comparing the expected (see Patients and methods) and the observed results. For this purpose, the percentage of responders was calculated for all available patients who entered the trial with a post-study drug available measurement. Patients who withdrew from the study because of lack of efficacy were considered as non-responders. Table 2 shows the percentage of responders per treatment subgroup. The percentages of responders with respect to pain assessment in the placebo group (26 out of 119, 22%) and in the piroxicam 20 mg group (52 out of 107, 49%) were close to those expected (20 and 50%, respectively). Moreover, the s.d. of the changes in the functional index (from 5.7 to 6.6, see Table 3) and the mean treatment effect [differences in the mean changes of the functional index between an active treatment group and the placebo (from 3.0 to 4.0, see Table 3)] were also close to those expected and predefined (5.85 and 3.0, respectively). The percentages of responders in the meloxicam groups [62 out of 117 (53%) and 60 out of 122 (49%) in the 15 and 22.5 mg meloxicam groups, respectively] were statistically significantly different from the placebo group ($P = 0.001$) and very similar to the piroxicam 20 mg group. Table 3 shows the changes in each variable by the end of the 6 weeks.

The latent period before the onset of activity of each NSAID group was estimated by analysis of two clinical variables (pain and functional disability) over time. This showed that all the active groups diverged from the placebo group after 1 week (data not shown).

Long-term (1 yr) efficacy. The analyses after 1 yr (conducted in a similar manner to those after 6 weeks of therapy) reached comparable results (see Tables 2 and 3). In particular, there was a statistically significant
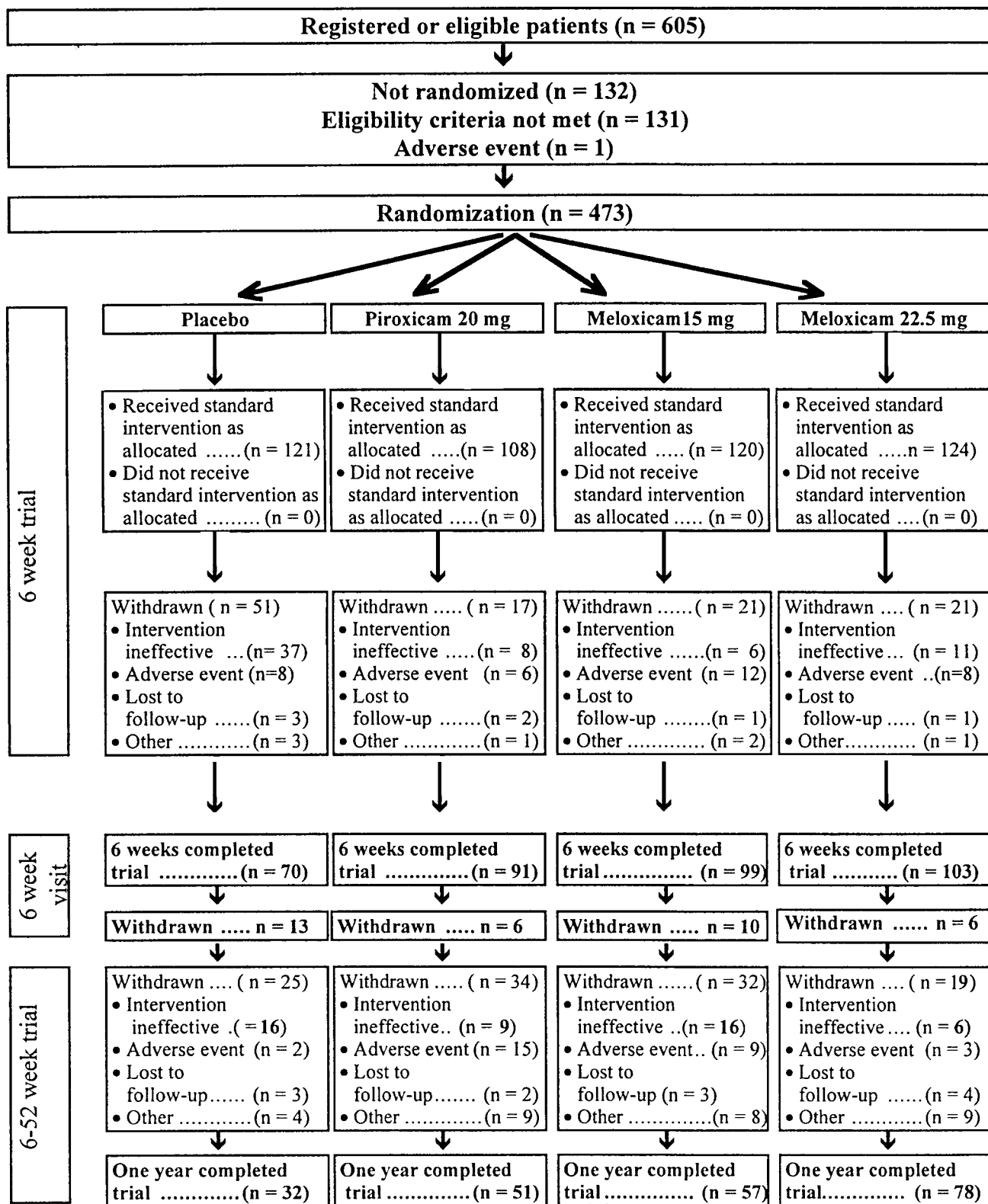
FIG. 1. Patients and study course.

TABLE 1. Baseline characteristics of the 473 randomized and treated ankylosing spondylitis patients, by treatment group

| Characteristic | Treatment group[b] | | | | |
	Placebo $n = 121$	P 20 mg $n = 108$	M 15 mg $n = 120$	M 22.5 mg $n = 124$	P[c]
Age (yr)	40 ± 12[a]	44 ± 13	44 ± 12	42 ± 12	0.04
Sex male (%)	72	77	79	85	NS
Body mass index	26 ± 4	26 ± 4	26 ± 4	25 ± 4	NS
Disease duration (yr)	12 ± 9	12 ± 11	13 ± 9	12 ± 10	NS
History of peripheral articular disease (%)	29	30	25	27	NS
History of acute anterior uveitis (%)	26	28	26	29	NS
Family history of spondylarthropathy (%)	35	28	39	42	NS
B27 HLA antigen (%)	90	84	80	91	NS
Outcome variables					
Overall assessment					
VAS (mm)	62 ± 20	65 ± 19	62 ± 20	65 ± 18	NS
Pain					
VAS (mm)	72 ± 17	72 ± 15	69 ± 18	72 ± 14	NS
Function					
Functional index	16 ± 7	15 ± 6	15 ± 7	15 ± 6	NS
Inflammation					
Morning stiffness (min)	88 ± 77	80 ± 72	77 ± 68	86 ± 77	NS
Sleep disturbance: yes (%)	79 (66)	80 (74)	71 (59)	78 (63)	NS
Range of motion					
Schober test (cm)	12.8 ± 1.5	12.8 ± 1.5	12.7 ± 1.5	12.7 ± 1.8	NS
Chest expansion (cm)	3.8 ± 2.2	3.5 ± 2.2	3.8 ± 2.2	3.5 ± 1.9	NS

[a]Values given are either mean $\pm$ S.D. or percentage.
[b]P, piroxicam; M, meloxicam.
[c]P is the statistical significance determined by either analysis of variance or χ^2 test; NS, not significant.

TABLE 2. Percentage of responders[a] in selected outcome variables at week 6 and week 52 in ankylosing spondylitis patients receiving either placebo ($n = 121$), piroxicam 20 mg ($n = 108$), meloxicam 15 mg ($n = 120$) or meloxicam 22.5 mg ($n = 124$)

| Variable | After 6 weeks | | | | After 1 yr | | | |
	Placebo	P 20 mg	M 15 mg	M 22.5 mg	Placebo	P 20 mg	M 15 mg	M 22.5 mg
Overall assessment	21	43[b]	50[b]	47[b]	17	37[b]	50[b,c]	43[b]
Pain (VAS mm)	22	49[b]	53[b]	49[b]	16	39[b]	50[b]	46[b]
Functional index	9	22[b]	28[b]	33[b]	13	24[b]	30[b]	33[b]

[a]A responder was defined by a decrease of at least 50% in the evaluated variable and no discontinuation during the study period because of inefficacy.
[b]Statistical significance ($P < 0.0167$) when compared with placebo.
[c]Statistical significance ($P < 0.05$) when compared with piroxicam.

TABLE 3. Mean changes in the clinical and biological variables during the first 6 weeks and the 1 yr of the trial in ankylosing spondylitis patients receiving either placebo, piroxicam 20 mg, meloxicam 15 mg or meloxicam 22.5 mg

| Variable | After 6 weeks | | | | After 1 yr | | | |
	Placebo	P 20 mg	M 15 mg	M 22.5 mg	Placebo	P 20 mg	M 15 mg	M 22.5 mg
Overall assessment (VAS mm)	-3 ± 29	-26 ± 28[a]	-26 ± 27[a]	-25 ± 29[a]	$+2 \pm 31$	-21 ± 30[b]	-25 ± 29[b]	-26 ± 30[b]
Pain (VAS mm)	-15 ± 27	-32 ± 27[a]	-32 ± 28[a]	-34 ± 26[a]	-11 ± 28	-29 ± 28[b]	-31 ± 30[b]	-33 ± 27[b]
Function								
Functional index	0.6 ± 6.6	-2.4 ± 5.7[a]	-3.1 ± 6.1[a]	-3.4 ± 6.0[a]	$+1.5 \pm 7.8$	-1.7 ± 7.4[b]	-3.1 ± 7.2[b]	-3.1 ± 7.0[b]
Inflammation								
Morning stiffness (min)	-5 ± 74	-21 ± 74	-25 ± 61[b]	-36 ± 74[b]	2 ± 74	-26 ± 66	-23 ± 68[b]	-42 ± 77
Sleep disturbance: yes (%)	60%	28%[b]	34%[b]	23%[b]	62%	34%[b]	36%[b]	27%[b]
CRP (mg/l)	$+4.2 \pm 13.6$	-1.6 ± 11.5[b]	$+0.2 \pm 15.9$	$+0.7 \pm 11.8$	6.0 ± 14.2	0.3 ± 17.0	-3.0 ± 16.1[b]	-2.4 ± 15.7[b]
Range of motion								
Schober test (cm)	0.1 ± 1.14	0.3 ± 1.1	0.3 ± 1.0	0.4 ± 1.3	0.1 ± 1.6	0.3 ± 1.3	0.3 ± 1.2	0.4 ± 1.4
Chest expansion (cm)	-0.2 ± 1.5	0.3 ± 1.5	0.3 ± 1.5	0.7 ± 2.0	-0.3 ± 1.6	0.5 ± 1.6[b]	0.3 ± 1.2[b]	-0.7 ± 1.9[b]

[a]Statistical significance ($P < 0.0167$) when compared with placebo.
[b]Statistical significance ($P < 0.05$) when compared with placebo.

difference between the placebo and each of the three active groups for most of the outcome variables. However, there was no difference between the three active groups, except for the patient's overall assessment (percentage of responders), with a statistically significant difference in favour of meloxicam 15 mg when compared to piroxicam. The life table analysis in which the event was defined by the discontinuation of the study drug because of inefficacy shows a highly statistically significant difference between placebo and each of the three active groups without any difference between the three active groups (Fig. 2a). At the end of the study, 66 (55%), 22 (20%), 28 (23%) and 20 (16%) patients discontinued prematurely due to lack of efficacy in the placebo, piroxicam 20 mg, meloxicam 15 mg and meloxicam 22.5 mg groups, respectively. The life table analysis in which the event was defined by the discontinuation of the study drug whatever the reason for discontinuation showed similar results (highly statistically significant difference between placebo and each of the three active groups); moreover, there was also a statistically significant ($P < 0.05$) difference in favour of meloxicam 22.5 mg when compared to either piroxicam 20 mg or meloxicam 15 mg. The percentages of patients who discontinued the study drug for whatever reason were 74, 53, 53 and 37% in the placebo, piroxicam 20 mg, meloxicam 15 mg and meloxicam 22.5 mg groups, respectively.

One year vs 6 weeks results. The numbers of responders observed after 1 yr *vs* 6 weeks are summarized in Table 4. The kappa index of agreement was 0.58, 0.65 and 0.71 for pain, patient's global assessment and functional index, respectively. Moreover, the kappa intraclass coefficient of correlation between the changes observed after 1 yr *vs* 6 weeks was 0.85, 0.87 and 0.83 for pain, patient's global assessment and functional index, respectively.

The life table analysis focused on the subgroup of the 328 patients still taking the trial drug after week 6. Outcome was defined by the discontinuation of the study drug, due to lack of efficacy between week 6 and week 52. The data reveal an inter-group statistically significant difference ($P < 0.01$, log rank test). Compared to placebo, the relative risk of discontinuation of the study drug was statistically significantly lower: 0.37 ($P = 0.013$) and 0.22 ($P = 0.0001$) for the piroxicam 20 mg and meloxicam 22.5 mg, respectively, but did not reach statistical significance [0.64 ($P = 0.17$)] for meloxicam 15 mg. There was no statistically significant difference between piroxicam and both meloxicam groups. However, there was a statistically significant difference in favour of meloxicam 22.5 mg when compared to meloxicam 15 mg ($P = 0.01$).

Assessment of tolerability

During the 1 yr of the trial, 159 patients experienced at least one adverse event which was classified by the investigator as having a reasonable possibility that it was caused by the study drug, without any statistically significant difference between the different groups [32

(26%), 41 (38%), 41 (34%), 45 (36%) with placebo, piroxicam 20 mg, meloxicam 15 mg and meloxicam 22.5 mg, respectively]. At the end of the trial, the number of patients withdrawn due to adverse events during the whole trial period was lower with placebo [10 patients (8%)] and meloxicam 22.5 mg [11 patients (9%)] than with meloxicam 15 mg [21 patients (18%)] and piroxicam 20 mg [21 patients (19%)]. However, the log rank test did not reach the level of statistical significance ($P = 0.08$) (see Fig. 2b). Upper gastrointestinal disorders were the most common adverse events. The life table analysis in which the event was defined by the occurrence of any upper gastrointestinal adverse event during the 1 yr of the study showed a statistically significant difference (log rank test, $P = 0.02$) between the four study groups (13, 32, 18 and 20% in the placebo, piroxicam 20 mg, meloxicam 15 mg and meloxicam 22.5 mg groups, respectively). A statistically significant difference was only observed with piroxicam 20 mg when compared to placebo ($P = 0.004$). The analysis focused on the three active NSAID groups showed a statistically significant difference between the two meloxicam groups and piroxicam ($P < 0.05$). A duodenal ulcer or gastric ulcer confirmed by endoscopy occurred in five patients during the trial: no ulcer in the placebo group, two duodenal ulcers and one gastric ulcer with melaena in the piroxicam 20 mg group, one duodenal ulcer in the meloxicam 15 mg and one duodenal ulcer in the meloxicam 22.5 mg group. An additional case of ulcer was reported by the investigator in the piroxicam group based on very suggestive clinical symptoms, but without endoscopic confirmation (patient's refusal).

Table 5 summarizes the adverse events observed in the placeo and in the active NSAID groups as well as the period of the first occurrence (week 0–week 6 *vs* week 6–week 52). This table shows that although most of the side-effects occurred during the first 6 weeks of the study, new additional side-effects were also reported between week 6 and 52. These appeared to be NSAID related since the percentage of gastrointestinal adverse events increased in a higher proportion in the active NSAID groups than in the placebo group. Indeed, the gastrointestinal NSAID effect can be estimated by the differences in the percentage of gastrointestinal adverse events occurring in the NSAID and placebo groups. During the first 6 weeks of the study, drug-related gastrointestinal adverse events were observed in 10 (9%) patients in the placebo group and in 62 (19%) in the NSAID group, i.e. a gastrointestinal NSAID effect of $19 - 9 = 10\%$. The same approach applied in the observed results at 1 yr shows that this gastrointestinal effect is 11% ($17 - 6\%$). This difference is due to the fact that more additional gastrointestinal adverse events occurred in the NSAIDs group [40 (17%)] than in the placebo group [3 (6%)] between week 6 and week 52, i.e. a gastrointestinal NSAID effect of 11%. In this study, this is particular true with regard to the observed gastro-duodenal ulcers in the piroxicam group (no ulcer during the first 6 weeks and 4 in the 6–52 week period).
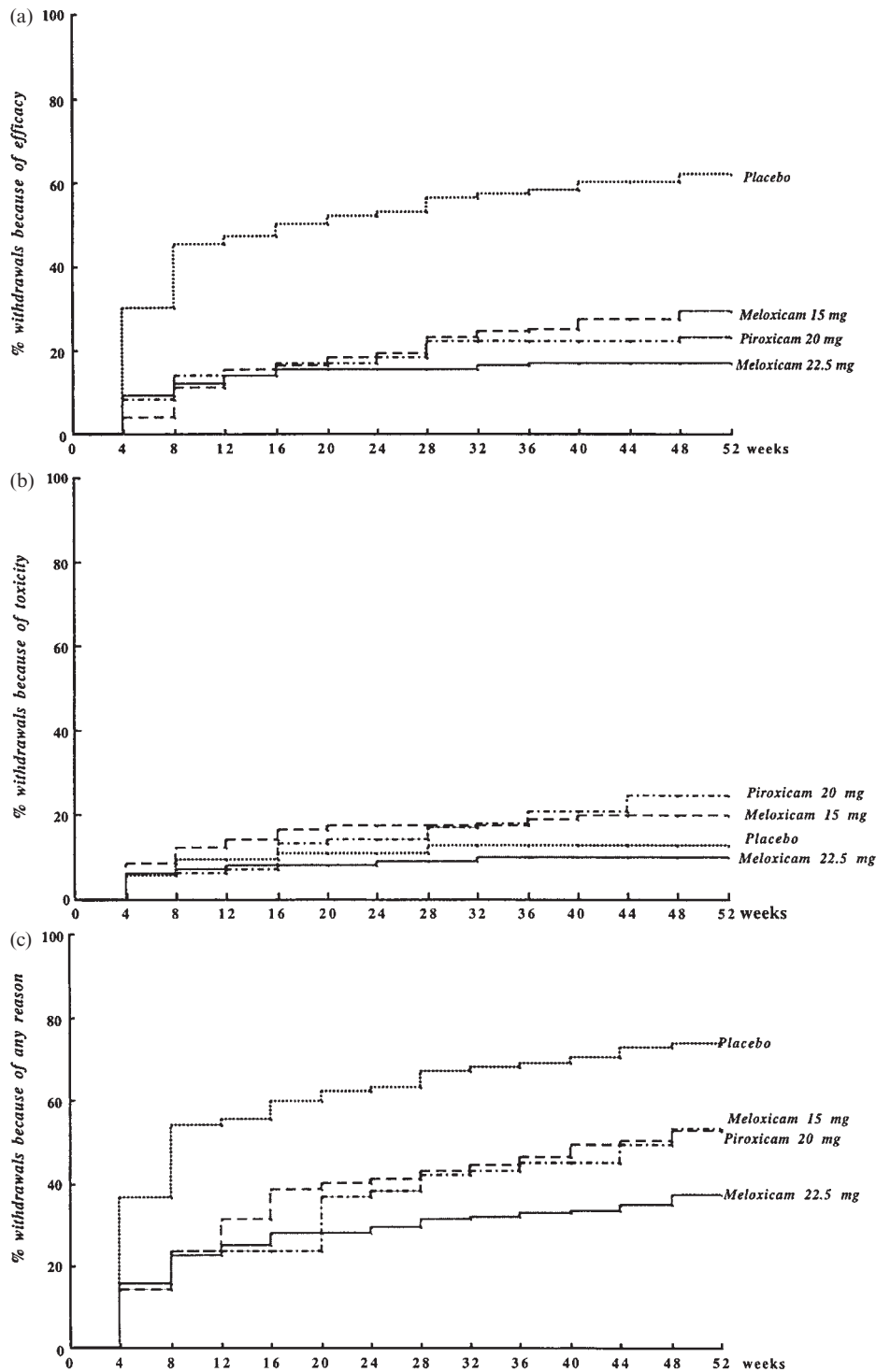
FIG. 2. Percentage who had to discontinue the study drug in ankylosing spondylitis patients receiving either placebo ($n = 121$), piroxicam 20 mg ($n = 108$), meloxicam 15 mg ($n = 120$) or meloxicam 22.5 mg ($n = 124$).

Discussion

This placebo-controlled study suggests that a 1 yr trial may provide more data than a 6 week investigation, giving more information regarding both the efficacy and tolerability of NSAIDs in this condition.

The main baseline characteristics of the studied patients are very similar to those previously reported in other clinical and epidemiological studies of ankylosing spondylitis. These results, together with the fact that the changes during the study in the main variables (i.e. pain, functional index and overall assessment of disease

TABLE 4. Number of responders[a] at 1 yr vs week 6 for the three selected outcome variables in the 473 ankylosing spondylitis patients

		Pain (VAS) Week 6		Patient global assessment (VAS) Week 6		Functional index Week 6	
		No	Yes	No	Yes	No	Yes
Week 52	No	236	31	251	28	234	27
	Yes	62	137	48	138	22	84

[a]A responder was defined as an improvement of at least 50% in the evaluated variable.

activity) in the inactive (placebo) and active (piroxicam) groups are similar to those expected, strengthen the validity of the trial.

In terms of evaluation of the efficacy, and based on the data obtained in our study, it is interesting to evaluate whether our conclusions might differ with the duration of the study. The 6 week results on the primary outcome variables, i.e. mean changes or percentage responders in pain, patient's global assessment and functional index, suggest that the three active groups (piroxicam 20 mg, meloxicam 15 mg and meloxicam 22.5 mg) do not differ and, consequently, that meloxicam 15 mg could represent the optimal daily dosage to be used in ankylosing spondylitis. Based on the 52 week results on the same parameters, the conclusions might be that most information obtained at 1 yr was in fact given at week 6 and, consequently, that a 52 week trial is useless to evaluate the efficacy of a new NSAID. However, the conclusions might be different if the outcome measure is not only focused on the conventional ones (mean changes and percentage responders), but also on the percentage of patients still taking the studied drug over time.

The life table analysis in which the event is defined by the percentage of patients who have to discontinue the study drug because of lack of efficacy might be more sensitive when applied to longer duration studies in this chronic inflammatory disorder. Such an approach is frequently used to evaluate the long-term utility and/or efficacy of drugs in rheumatoid arthritis [26, 27]. In our study, we were unable to detect a statistically significant difference between the three active drugs when applied from baseline to week 52, but were able to detect a difference between 22.5 mg and 15 mg meloxicam daily dosage when this analysis focused on the period between week 6 and week 52. Since it might be difficult to define precisely the reason for discontinuation of a drug, the other proposed methodology is to evaluate the percentage of withdrawals over time whatever the reason for discontinuation. Using this methodology, we were able to detect a difference between active NSAIDs (in favour of meloxicam 22.5 mg when compared either to piroxicam 20 mg or to meloxicam 15 mg). These results suggest that, in some patients, a 22.5 mg meloxicam daily dose would be of more value than a 15 mg daily dose during the painful flare of the disease and, consequently, that a 52 week trial is useful to evaluate the efficacy of a new NSAID. Finally, one could consider that a short-term study (i.e. a 6 or even a 2 week study) is sufficient to confirm the efficacy of a new NSAID; at variance, a longer duration study seems to be more appropriate to detect a difference between two active NSAIDs or between two different dosages of a given NSAID.

In terms of evaluation of the tolerability, it also seems interesting to evaluate whether our conclusions might differ with the duration of the study. The detailed analysis of adverse events suggests that a 1 yr trial is of greater value than a 6 week one in order to define the tolerability of NSAIDs in ankylosing spondylitis. For example, the gastrointestinal treatment effect, i.e. the differences in the percentages of observed gastrointestinal adverse events between active drugs and the placebo, was 10% at week 6 and 11% between week 6 and year 1. These results clearly confirm that drug-related gastrointestinal adverse events can occur after the first 6 weeks of the study [28]. The life table analysis evaluat-

TABLE 5. Number (Kaplan–Meier product limit estimate as percentage) of patients with drug-related adverse events (AE) during the 1 yr of the study by treatment group and study period of the first occurrence

	0–52 weeks		Study period of the first occurrence 0–6 weeks		6–52 weeks	
Side-effects	Placebo	Active NSAID	Placebo	Active NSAID	Placebo	Active NSAID
Evaluated patients	121	352	121	352	57	271
Patients with any AE	32 (33)	127 (42)	26 (24)	83 (25)	7 (13)	61 (27)
Gastrointestinal (GI) AE	14 (16)	91 (29)	10 (9)	62 (19)	3 (6)	40 (17)
Upper GI AE[a]	11 (13)	71 (23)	8 (8)	49 (14)	2 (4)	31 (14)
PUBs	0 (0)	6 (2)	0 (0)	2 (<1)	0 (0)	4 (2)
Central and peripheral nervous system disorders	8 (9)	15 (5)	7 (9)	11 (3)	1 (2)	5 (2)
Skin and appendages	4 (4)	14 (5)	4 (4)	10 (3)	1 (2)	5 (2)
Respiratory system disorders	2 (2)	2 (<1)	1 (<1)	1 (1)	1 (2)	1 (<1)

PUB is perforation of ulcer, ulcer, bleeding of the upper gastrointestinal tract. All PUBs were confirmed by endoscopy, except one case in the piroxicam group due to patient refusal.

[a]Only upper GI AE as referred terms known to be potentially related to NSAID toxicity were taken into account (PUB/gastritis/abdominal pain/dyspepsia/nausea/vomiting).

ing the percentage of patients suffering from an upper gastrointestinal adverse event during the 1 yr of the study permitted us to demonstrate not only a statistically significant difference between an active NSAID (i.e. piroxicam 20 mg) and placebo (with a more toxic profile of the active NSAID), but also an interactive NSAID group difference (i.e. a more toxic profile of piroxicam 20 mg when compared to meloxicam 22.5 mg). Moreover, this study also suggests that severe gastrointestinal adverse events such as perforation, ulcer or bleeding can be missed during a 6 week study. This was particularly true in the piroxicam group in which all the ulcers were recognized between week 6 and week 52. These results suggest that a 1 yr study is more appropriate than a 6 week one to detect a difference in the tolerability between placebo and active NSAID, but also between two active NSAIDs.

Finally, this 1 yr duration trial highlights the relatively high proportion of patients who can take placebo during a 1 yr study. These results may also question the rationale for continuous daily intake of NSAIDs in ankylosing spondylitis. It is obvious (and this study confirms) that an NSAID is of most value in the treatment of a painful flare of the disease. It is also obvious that the natural history of ankylosing spondylitis is not uniform; periods of remission intersperse with episodes of flare. Therefore, it may be sensible to restrict NSAID therapy to the duration of the flares and to discontinue the drug thereafter. The occurrence of late gastrointestinal adverse events demonstrated in this trial is also an argument in favour of a restricted duration of treatment. In this study, the patients were asked to take their NSAID every day whatever the level of symptoms; other clinical trials are required in order to evaluate both the long-term effect of different regimens of NSAID intake and, in particular, a 'continuous' vs an 'on-request' regimen.

Acknowledgements

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