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Comparative Study of the Efficacy and Safety of Aceclofenac and Tenoxicam in Rheumatoid Arthritis

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Summary **To compare the efficacy and safety of aceclofenac (AC) and tenoxicam (TX) in the treatment of rheumatoid arthritis (RA), a multicentric parallel, randomized, double-blind trial of three months duration was performed in 292 patients: 145 were randomized to the AC treatment group and 147 to the TX treatment group. The trial was completed by 237 (81.1%) patients. Both treatment groups showed amelioration of clinical parameters monitored at 15 days, and this improvement continued until the end of the trial, no statistically significant differences being observed between AC and TX. Twenty-four patients (8.2%, 12 AC and 12 TX) did not complete the trial because of inefficacy, and 15 because of side effects (5.1%, 6 AC and 9 TX), in 7 of them due to gastrointestinal intolerance (2,4%, 1 AC, 6 TX, p=0.052). These data demonstrate that AC shows similar efficacy to TX in the treatment of rheumatoid arthritis and better safety profile than TX, mainly regarding gastrointestinal tolerability.**

Key words **Aceclofenac, Tenoxicam, Rheumatoid Arthritis, NSAID.**

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been the mainstay of symptomatic treatment of RA for several decades (1). There is still considerable room, however, for improvement in the relationship between efficacy and tolerability.

AC is a new NSAID of the phenylacetic acid family. Previous experimental studies have demonstrated that AC possesses potent analgesic and anti-inflammatory properties (2,3). Administered by the oral route, its bioavailability is greater than 90%, reaching maximum plasma levels one hour after administration, with a plasma half-life of 4 to 6 hours (2). In previous studies, aceclofenac has been shown to have clear anti-inflammatory and analgesic properties and good safety profile (4,5).

The aim of the present study was to evaluate the efficacy and tolerability of AC in the treatment of RA, in comparison to TX, a recently introduced NSAID with establised efficacy and tolerability (6-8).

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MATERIALS AND METHODS

Design

Sixteen Rheumatology Units located in Spain participated in a parallel, comparative, randomized, double-blind trial of 3 months duration. The required size of the total sample in order to obtain statistically significant differences was estimated at 242 patients (9). Each center contributed a similar number of patients. The design of the trial was approved by the Ethical Committees of the hospitals in which the trial took place, as well as by the Spanish Health Ministry. The design, procedures and follow-up of the protocol (monitoring visits) were always carried out in accordance with the standard procedures of Good Clinical Practice.

Patients

Patients recruited were between 18 and 70 years, with RA that fulfilled the ARA 1987 classification criteria (10) and pain which was greater than 40 mm on a 100 mm visual analogue pain scale. Excluded from the study were patients who were pregnant or nursing, had undergone gastrectomy, suffered from peptic ulcer during the previous year, had an acute myocardial infarction or cerebral vascular accident within the previous four months, had uncontrolled arterial hypertension, respiratory or

cardiac or renal insufficiency (creatinemia greater than 1.5 mg/dL), haematological or hepatic disease of any origin, or a life expectancy of less than 2 years, were hypersensitive to any NSAID or had participated in another clinical trial during the previous three months. Other patients not eligible for the trial were those whose treatment previous to the trial included: gold sodium thiomalate for less than 6 months; methotrexate, chloroquine, D-penicillamine or salazopyrine for less than two months; corticosteroids for less than two months or at a dosage greater than 7.5 mg prednisone or equivalent per day for less than a month before entering the trial. A total of 292 patients were included in the trial; they all gave their informed consent to participate in the study.

Drug treatment

Patients were assigned in a double-blind randomized fashion to two treatment groups: group AC, which received tablets containing aceclofenac 100 mg every 12 h, and group TX, which received tablets containing placebo in the morning and tenoxicam 20 mg at night. Before the trial started, the patients discontinued treatment with all NSAIDs for the period of 7 days. During this period, the use of paracetamol was allowed at normal dosages to alleviate pain. Patients were then handed the drug assigned to them. The external appearance of the tablets was identical either containing placebo, aceclofenac or tenoxicam, in order to maintain the double-blind design of the trial. Intra-articular treatment with corticosteroids was not permitted during the trial. At each control visit, patients were required to return unused medication in order to ensure compliance of treatment.

Evaluation of efficacy

The efficacy of treatment was evaluated at baseline, 15 days, 1, 2 and 3 months by the Ritchie Index (RI) (11); a visual analogue pain scale (VAS) of 100 mm; and the grip strength (in mm Hg) of the right hand (GSR) and of the left hand (GSL), using a mercury sphygmomanometer inflated to a pressure of 30 mm Hg. In addition, spontaneous morning pain (MP), spontaneous nocturnal pain (NP) and pain on movement (PMO), were assessed on a semiquantitative scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe). Morning stiffness was assessed on a semiquantitative scale (0 = without stiffness, 1 < 30 min, 2 = > 30 to 120 min, 3 = > 120 min). ESR in the first hour was also evaluated at 1 and 3 months.

Table I: *General characteristics of the patients.*

	Group AC	Group TX
No. of patients	145	147
Male/female	32/113	26/121
Age (years)	56.8 ± 9.8 (26-70)	56.4 ± 10.1 (29-70)
RI	22.6 ± 10.3 (5-52)	22.8 ± 10.9 (5-52)
VAS (mm)	63.2 ± 13.2 (40-100)	62.3 ± 13.9 (40-100)
GSR (mm Hg)	80.8 ± 35.5 (30-205)	80.0 ± 38.7 (30-300)
GSL (mm Hg)	81.2 ± 35.7 (30-250)	82.5 ± 38.3 (30-300)
ESR (mm)	37.8 ± 23.43 (4-106)	35.6 ± 21.68 (2-115)
Hb (g/dL)	12.9 ± 1.4 (9.1-16.7)	13.1 ± 1.4 (8.516.6)

Values shown indicate mean ± standard deviation and range (in brackets). RI = Ritchie Index; VAS = visual analog pain scale; GSR = grip strength of the right hand ; GSL = grip strength of the left hand.

Evaluation of safety

Laboratory analyses were done at baseline, 1 month and 3 months and included: complete blood counts, plasma biochemistry (including creatinine, Na, K, Cl, lactate dehydrogenase and liver function tests) and urine analysis. Determination of fecal blood loss was carried out at every analysis and, when positive, repeated in order to assess persistent fecal blood loss which was a reason for terminating the trial.

Signs and symptoms of concomitant and intercurrent diseases and appearance of side effects were monitored at baseline, 15 days, 1, 2 and 3 months, when body weight and systolic and diastolic blood pressure were measured. Patients were asked to spontaneously report side-effects, and, when no side-effects was reported, a brief anamnesis was made in order to ensure their absence.

Statistical methods

The analysis of the data was carried out using the statistics program SPSS 4.0. For the study of quantitative variables, Student's test was used for the comparison of paired and independent data; qualitative variables were analysed by the Chi-squared and Wilcoxon tests (intragroup comparison) and the MannWhitney U-test (intergroup comparisons).

RESULTS

A total of 292 patients were included in the study, 145 were randomized to the AC treatment group and 147 to the TX treatment group. There were no appreciable differences between the two treatment groups with regard to the distribution of age or gender nor to any of the clinical parameters (Table I). All of the clinical parameters used to assess clinical efficacy improved in both treatment groups during the trial, significant differences with respect to the initial values being noted in all parame-

Table II: *Effects of AC and TX on directly assessed efficacy parameters during the course of treatment.*

	Group AC			Group TX		
	Basal N=145	15 days N=137	3 mths N=124	Basal N=147	15 days N=140	3 mths N=113
RI	22±10	18±12*	14± 9*	23±11	17±11*	12± 9*
VAS (mm)	63±13	51±21*	42±21*	62±14	50±19*	39±23*
GSR (mm Hg)	81±35	89±38*	94±44*	80±39	88±40*	99±43*
GSL (mm Hg)	81±36	87±37*	92±44*	82±38	87±36*	94±37*
	Basal	30 days	3 mths	Basal	30 days	3 mths
ESR (mm)	38±23	33±23*	31±24*	36±22	31±21**	29±21**

RI = Ritchie Index; VAS = visual analog pain scale; GSR = grip strength of the right hand; GSL = grip strength of the left hand.
* $p < 0.01$ vs basal. ** $p < 0.05$ vs basal.

ters evaluated at 15 days, and these differences continued throughout the three months of the trial (Tables II and III). No significant differences in any parameters were observed between the AC and TX groups at any time. A total of 24 patients (8.2%) discontinued the trial due to inefficacy, 12 (8.3%) in the AC group, and 12 (8.1%) in the TX group.

Arterial pressure and body weight measurement did not change in the two treatment groups during the trial (data not shown). Fecal blood loss was detected before treatment in 1 patient of the TX group. During the trial, fecal blood loss was detected in 4 patients in each group after one month of treatment and in one patient in each group after three months. Only one patient in the TX group discontinued the trial for this reason; in the remaining cases the fecal blood loss was transient and not accompanied by analytical or clinical indications of gastrointestinal haemorrhage.

Seventy-one patients (24.3%) presented adverse reactions, 35/145 (24.1%) in the AC group and 36/147 (24.4%) in the TX group, no difference being observed between the two groups. Gastrointestinal intolerance (epigastric pain, pyrosis, nausea) was the most frequent of the adverse events (27/145, 18.6% in the AC group and 25/147, 17.6% in the TX group) and did not differ between treatments. However, the number of premature withdrawals due to gastrointestinal intolerance was smaller in the AC group (1/145) than in the TX group (6/147) ($p = 0.05$); in this latter group, 1 patient showed persistent positive tests for occult fecal blood and 1 patient suffered gastric ulcer demonstrated by endoscopy (Table IV). The skin adverse effects were rashes in all cases (9/292, 3.1%), and their frequencies (6/145 in the AC group, 3/147 in the TX group) were not statistically different in the two treatment groups. There were 4 adverse central nervous system (CNS) reactions, all of them in the TX group, described as dizziness, and severe enough to suspend treatment in 2 patients.

Table III: *Effects of AC and TX on scored efficacy parameters during the course of treatment.*

		Group AC (*)			Group TX (*)		
Score		Basal N=145	15 days N=135	3 mths N=124	Basal N=147	15 days N=140	3 mths N=113
MP	0	8	16	34	8	22	43
	1	37	51	49	35	54	44
	2	50	47	33	56	38	20
	3	45	19	8	38	22	6
	4	5	3	0	10	4	1
PM	0	1	9	16	1	9	23
	1	16	54	58	29	45	59
	2	71	46	36	64	51	21
	3	53	26	13	44	30	11
	4	4	2	1	9	3	0
NP	0	26	46	53	22	51	64
	1	47	46	47	61	44	33
	2	38	30	16	47	35	14
	3	31	12	7	11	7	2
	4	3	3	1	6	2	1
MS	0	2	19	24	1	16	24
	1	45	61	59	48	66	59
	2	72	46	31	74	46	26
	3	26	11	10	24	11	5

Values shown indicate the distribution of patients in each group for any parameter monitored.
MP = morning pain; 1 = PM = pain on movement; NP = noctural pain; MS = morning stiffness. MP, PM and NP scoring: 0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe. MS scoring: 0 = no stiffness, 1 = < 30 min, 2 = 30-120 min, 3 = > 120 min.
(*) comparison of the distribution at 15 days and 3 months vs basal for all parameters: $p < 0.001$ by Wilcoxon matched-pairs signed rank test.

Fourteen patients (4.7%) showed an increase of liver blood tests, 9 (6.2%) in the AC group and 5 (3.4%) in the TX; 7 out of these 14 patients were on methotrexate therapy, 5/9 in the AC group and 2/5 on the TX group.

Table IV: *Adverse reactions and premature terminations due to adverse reactions.*

Type of reaction	No. of reactions		Premature terminations	
	AC	TX	AC	TX
Gastrointestinal	27	26	1*	6*
Rash	6	3	5	1
Dizziness	0	4	0	2
Others	2	3	0	0
	35	36	6	9

* Ac vs TX = p = 0.052

Table V: *Reasons for premature termination of the trial.*

Cause	No. of patients		
	Total	Group AC	Group TX
Inefficacy	24 (8.2%)	12 (8.3%)	12 (8.1%)
Adverse reactions	15 (5.1%)	6 (4.1%)	9 (6.1%)
Loss of follow-up	6 (2.0%)	3 (2.1%)	3 (2.0%)
Intercurrent disease	1 (0.3%)	0	1 (0.7%)
Voluntary withdrawal	9 (3.1%)	0	9 (6.1%)
Total	55	21	34

The increase was persistent in 5 (1.7%) patients, 3 in the AC group and 2 in the TX group (2/5 were on methotrexate therapy) and self-limited in the rest. Only 2 of the 14 patients with altered liver function tests showed an increase over twofold, but transient, of ALAT normal values (1 in the AC group and 1 in the TX group). No patient discontinued therapy due to hepatotoxicity.

The trial was completed by 237/292 patients (81.1%). It was not completed by 21/145 patients (14.4%) in the AC group and 34/147 (23.1%) patients in the TX group. The reasons for premature termination of the trial are detailed in Table V.

DISCUSSION

The results of this comparative, randomized double-blind study show that AC possesses similar efficacy and general tolerance to that of TX in the treatment of RA. Both drugs provide a rapid clinical response which was already significant 15 days after start of treatment. The rapid onset of the action of AC has been noted in previous studies (4,5) and is probably in part a consequence of its good pharmacokinetic properties. The clinical response was maintained throughout the three months of the trial and only 8.2% of the patients discontinued the trial because of inefficacy, a similar percentage for the two treatment groups. Nevertheless, 9 more patients in the TX group chose to abandon the trial for undefined reasons. It is possible that these 9 patients considered that therapy was not effective enough, and this would increase the rate of withdrawal due to lack of efficacy in the TX group to 14.3%, which is similar to the 17.8% reported by Atkinson et al. (8) in a comparative trial of tenoxicam and piroxicam in 102 rheumatoid arthritis patients.

A quarter of the patients in each group presented some adverse reaction, an incidence similar to the 23.9% reported by Caughey et al. (6) and the 31.4% reported by Atkinson et al. (8) for TX. Gastrointestinal intolerance was responsible for the majority of the side effects in both of our treatment groups and was the reason for 35% of withdrawals because of side effects. However, these gastrointestinal alterations were perhaps less severe in the AC group, with only one withdrawal for this reason compared to 6 in the TX group, including 1 patient with persistent positive tests for fecal blood loss and 1 patient with gastric ulcer in the last treatment group (TX). Therefore, although the frequency of gastrointestinal intolerance was similar in both groups, gastrointestinal withdrawals were more frequent in the TX group.

Slight, transient, increases of liver blood tests were observed in 3% of patients and slight, persistent, increases were observed in 1.7%. There were no withdrawals due to hepatic toxicity. Moreover, 50% of patients showing altered liver blood tests during follow-up were on methotrexate therapy. A quarter to a third of patients on methotrexate therapy showed liver toxicity (12).

In conclusion, AC has been shown to possess a similar efficacy to that of TX in the treatment of RA, but with a lower rate of voluntary withdrawal and good tolerability. Gastrointestinal tolerability appears to be somewhat better with AC than with TX, confirming that AC is effective and well tolerated in the treatment of RA.

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