Etoricoxib in ankylosing spondylitis: is there a role for active patients refractory to traditional NSAIDs?

J. Gratacós[1], M. Moreno Martínez-Losa[1], P. Font[2], C. Montilla[3], C. Fernández-Espartero[4], L.F. Linares[5], E. Brito[6], J.C. Oliva[7], E. Collantes-Estevez[2], and the Etoricoxib Study Group

[1]Rheumatology Unit, Hospital Universitario Parc Taulí, Sabadell, Spain;
[2]Rheumatology Unit, Hospital Universitario Reina Sofía, IMIBIC, Córdoba, Spain;
[3]Rheumatology Unit, Hospital Universitario de Salamanca, Spain;
[4]Rheumatology Unit, Hospital Universitario de Móstoles, Madrid, Spain;
[5]Rheumatology Unit, Hospital Virgen de Arrixaca, Murcia, Spain;
[6]Rheumatology Unit, Hospital Universitario Ramón y Cajal, Madrid, Spain;
[7]Statistics Department, Hospital Universitario Parc Taulí, Sabadell, Spain.

Abstract

Objective

To evaluate the efficacy of etoricoxib in patients with axial ankylosing spondyloarthritis (AS) refractory to traditional NSAIDs.

Methods

This was an open label, multicentric, randomised, prospective (4 weeks with and open extension to 6 months), non-controlled study. Consecutive patients with axial AS refractory to traditional NSAID eligible for anti-TNF-α therapy were selected. The primary outcomes were the rate of patients with good clinical response (not eligible for anti-TNF-α therapy after etoricoxib) and the Assessment of Spondyloarthritis International Society response criteria for biologic therapies (ASASBIO) response at 4 weeks. Secondary outcomes included: ASAS20 and 40 responses, ASDAS-CRP response, BASDAI, BASFI, back and night back pain, global patient and physician assessment of the disease, and biologic parameters like C-reactive protein (CRP) at 2, 4 weeks and 6 months.

Results

A total of 57 axial AS patients were recruited, 46 men, with mean age of 43 years. After 4 weeks of treatment, 26 patients (46%) achieved a good clinical response and 11 (20%) an ASASBIO response. These results at 24 weeks were 19 (33%) and 13 (23%) respectively. All individual clinical variables improved significantly after 4 weeks of treatment. CRP serum levels decreased after 4 weeks but reached no statistical significance, although 30% of patients showed a normalisation of CRP.

Conclusion

Etoricoxib provided a clear clinical improvement in around a third of patients with axial AS refractory to traditional NSAIDs. Special care should be required when deciding to start anti-TNF-α therapy; it seems reasonable to keep in mind these results of etoricoxib treatment.

Key words

ankylosing spondylitis, etoricoxib, anti-TNF therapy, BASDAI, BASFI, safety, open label, ASASBIO, ASDAS-CRP, satisfaction

Jordi Gratacós, MD, PhD
Mireia Moreno Martínez-Losa, MD, PhD
Pilar Font, MD, PhD
Carlos Montilla, MD
Cruz Fernández-Espartero, MD
Luis Francisco Linares, MD, PhD
Elia Brito, MD, PhD
Juan Carlos Oliva, statistician
Eduardo Collantes-Estevez, MD, PhD

The Etoricoxib Study Group:
Xavier Juanola, Hospital Universitario de Bellvitge, Barcelona;
Juan Mulero, Hospital Puerta del Hierro, Madrid;
Rubén Queiro, Hospital Universitario Central de Asturias, Oviedo;
Rosa Morlá, Hospital de San Pau i Santa Tecla, Tarragona;
Estefania Moreno Ruzafa, Hospital San Rafael, Barcelona;
Rosario García-Vicuña, Hospital La Princesa, IIS-IP, Madrid;
Joan Calvet Fontova, Hospital Universitario Parc Taulí, Sabadell;
Raimón Sanmartí, Hospital Clínic i Provincial, Barcelona.

Please address correspondence to:
Jordi Gratacós,
Rheumatology Unit,
Hospital Universitario Parc Taulí
Parc Taulí 1,
08208 Sabadell,
Barcelona, Spain.
E-mail: jgratacosmas@gmail.com

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Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic condition with an estimated prevalence of approximately 0.2% (1). The management of axial manifestations usually requires full doses of non-steroidal anti-inflammatory drugs (NSAIDs) for long periods of time (2-4). NSAIDs are an effective symptomatic treatment for these patients, although there is controversy regarding to a possible disease-modifying effect of these drugs (5). Unfortunately, no clear benefit has been demonstrated with disease-modifying anti-rheumatic drugs (6-8).

On the other hand, in the last few years, treatment with anti-TNF-α agents have shown remarkable efficacy for NSAID-refractory AS patients, suggesting that they could even modify the course of the disease (9-11). However, anti-TNF-α therapy is associated with important economic costs and potential toxicity (12, 13). As a result, its use is often limited to NSAID-refractory patients (14, 15).

Etoricoxib is a cyclooxygenase-2 (COX-2) selective inhibitor NSAID that has an indication for the symptomatic treatment of AS at a recommended daily dose of 90 mg. Most guidelines and consensus recommendations consider etoricoxib as efficacious as traditional NSAIDs, probably based on some published data (16). These documents also point out that the gastrointestinal (GI) safety profile is better for etoricoxib than for traditional NSAIDs (17). Therefore, it is suggested that etoricoxib could be an alternative for AS patients at high GI risk (18). Interestingly, recent data have shown that etoricoxib is a safe drug for the treatment of symptomatic AS and noticeably more effective that traditional NSAIDs, at least in the short term (19).

Nevertheless, its role as an anti-TNF-sparing agent in NSAID-refractory active AS patients or its possible disease-modifying effect is unclear (20).

The aim of this study was to assess clinical and biological response to etoricoxib in AS patients eligible for anti-TNF-α therapy.

Methods

Study design

This was a pragmatic, multicentric, open-label 4-week clinical trial with an extension period of 6 months. The study was approved by the different ethic committees of participating centres and all patients gave informed written consent.

Patients selection and data acquisition

All patients were required to 1) fulfil New York modified criteria of AS (21), 2) had a predominantly axial form, 3) be on stable and full doses of NSAIDs and 4) be eligible for anti-TNF-α therapy according to the Spanish Society of Rheumatology consensus statement of anti-TNF-α therapy for AS (22), defined as Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)>4 and physician's global assessment of disease activity using a visual analogue scale (VAS) >4 despite full doses of two different classical NSAIDs during a period of 3 months (14). Exclusion criteria included: active peripheral arthritis, the presence of active extra-articular manifestations, diagnosis of other inflammatory diseases, previous use or contraindications to etoricoxib, and previous use of anti-TNF-α therapy.

The included patients were then assigned to a stable dose of etoricoxib 90 mg per day for 4 weeks. There was not washout period. Patients achieving a good clinical response to etoricoxib at week 4, defined as no longer satisfying anti-TNF-α therapy criteria, were followed-up in an open extension study for 6 months.

Clinical and laboratory measurements were carried out at baseline, 2 and 4 weeks and 6 months.

Variables

The primary outcomes were the proportion of patients fulfilling at 4 weeks the Assessment of Spondyloarthritis International Society (ASAS) response criteria for biologic therapies (ASASBIO) (23) defined as an improvement of (a) at least 50% or 2 units (on a 0–10 scale) of the BASDAI and b) expert opinion; and the rate of patients with good clinical response (patients eligible for anti-TNF-α therapy according to national guidelines that do not fulfil these criteria after etoricoxib treatment).

Secondary outcomes included the proportion of patients with ASASBIO and

good clinical response at 6 months; the ASAS working Group response (ASAS20/40) (24), the Ankylosing Spondylitis Disease Activity Score (ASDAS) C-reactive protein (ASDAS-CRP), BASDAI and the Bath Ankylosing Spondylitis Functional Index (BASFI) (25) scores, patient's global assessment of the disease (0–10 VAS scale), physician's global assessment of the disease (0–10 VAS scale), back night pain (0–10 VAS scale), daily global pain (0–10 VAS scale) and the CRP (mg/L) at 4 and 24 weeks.

Finally, the assessment of health-related quality of life was measured by the Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire (Spanish validated version) (26) and the degree of satisfaction and the willingness to continue the drug using a four-point (0–3) Likert scale (0=no, 1=mild, 2=good and 3=excellent).

We also registered sociodemographic variables including age and sex and AS related variables as disease duration.

Statistical analysis

To describe the sample, we used the distribution of frequencies, the mean and standard deviation, or the median and interquartile range, depending on the variable distribution. Intention-to-treat analysis was performed on clinical data, showing results with their 95% confidence interval (CI). Mann-Whitney U-test and Wilcoxon signed rank test for paired data were performed for the analysis.

Results

We recruited 57 axial AS patients, 46 of whom were men, and with a mean age of 43.2±10.4 (range 22-69) years. At inclusion, all patients had previously received full doses of NSAIDs (11 naproxen, 14 diclofenac, 21 indomethacin, 7 ibuprofen, 3 oxicams and 1 phenylbutazone). Mean BASDAI score at study entry was 60±15. Table I summarises the baseline characteristics of the included patients.

A total of 53 patients completed the 4-week treatment period, 26 patients achieved a good clinical response at week 4, and 23 of them completed the 6-month extension period (Fig. 1).

Table I. Baseline characteristics of study patients*.

Variable	n=57
Age (years)	43.2 ± 10.4
Sex male/female (%)	46/11 (80%/20%)
Disease duration (years)	12 ± 5
BASDAI	6 ± 1.5
Spinal night pain (VAS)	6.6 ± 2.1
Patient's global assessment of disease activity (VAS)	6.42 ± 1.9
Physician's global assessment of disease activity (VAS)	6.2 ± 1.4
CRP (mg/L)	11.1 ± 13
BASFI	5 ± 2.1
ASQoL	10.1 ± 4.4

*Results are expresses as mean ± standard deviation otherwise is indicated.
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; VAS: visual analogue scale; CRP: C-reactive protein; mg=milligram; L: litre; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQoL: Ankylosing Spondylitis Quality of Life.

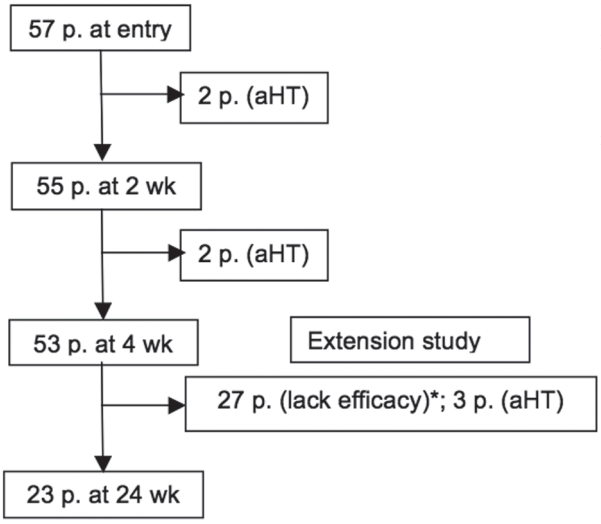

Fig. 1. Patients flow chart.
p: patients; aHT: arterial hypertension; wk: weeks
*Lack of efficacy was defined as not achieving a good clinical response.

Primary outcomes

We found that 22 patients (38%) and 6 (11%) showed a good clinical response and ASASBIO, respectively, at week 2. After 4 weeks of treatment, 26 (46%, 95% CI 33–59) and 11/57 patients (20%, 95%CI 10–30) achieved a good clinical response and ASASBIO, respectively (Fig. 2). Between weeks 2 and 4, one patient lost good clinical response and 8 achieved it in this period.

Secondary outcomes

At the end of the extension period (24 weeks), 19 patients (33%) showed a good clinical response and 13 (23%) achieved ASASBIO response (Fig. 2). Nineteen out of 26 patients (73%) who were included in the extension study maintained the good clinical response and did not fulfil criteria for anti-TNF-α treatment.

Similarly, 35 (61%) and 31 patients (54%) achieved ASAS20 and ASAS40 response at week 4, respectively. The ASDAS-CRP baseline score (3.3±0.8) improved significantly at 4 and 24 weeks 2.5±0.8 and 1.6±0.5 respectively ($p<0.001$). At study entry, 90% of patients showed high (33 patients) or very high (19 patients) disease activity determined by ASDAS-CRP. Twenty-five percent of patients presented inactive (5 patients) or moderate disease activity (9 patients) at week 4. These results were maintained up to 24 weeks (Fig. 3).

BASDAI, BASFI and all clinical variables started to decrease after 2 weeks of treatment, achieving in all cases an improvement of approximately 30% at 4 and 24 weeks (Table II).

Baseline CRP levels were 11.1±13 mg/L; 28 patients (50%) showed high CRP levels (≥5 mg/L) upon study entry (Table I). CRP decreased, mainly after

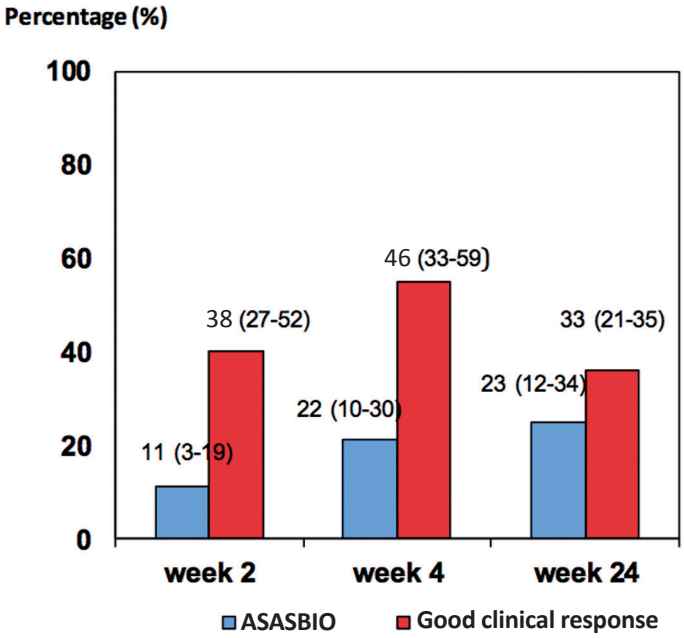

Fig. 2. Comparison of the proportion of patients with ASAS-BIO (blue colour) and good clinical response defined as not achieving criteria for anti-TNF treatment (red colour) at 2 wk, 4 wks and 24 wks respectively. Results are expressed as percentage and 95% confidence interval.

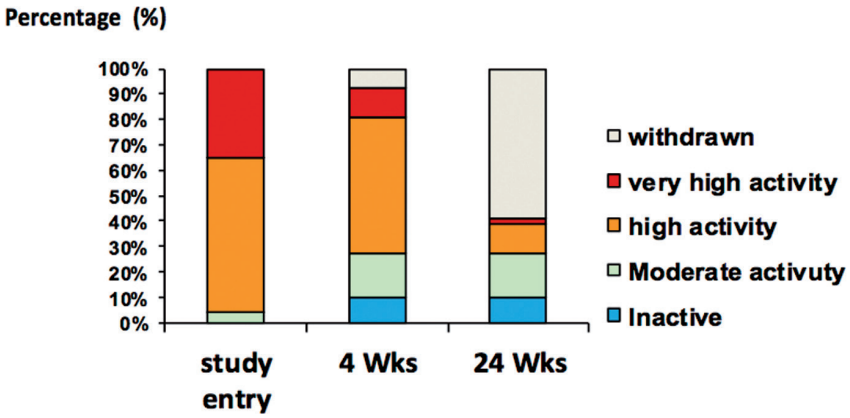

Fig. 3. ASDAS-CRP response during the study follow-up.
Withdrawals from the study were due to toxicity or lack of efficacy. At 24 wks 27/30 (90%) of patients were withdrawn because they did not achieve a good clinical response at week 4.

4 weeks of treatment, and almost 30% of patients showed a normalisation of CRP values. However, the decrease in CRP values did not reach statistical significance (from 11.1±13 mg/L to 8.3±10 mg/L, $p>0.050$) (See Table II). Patients with high CRP reported a slightly better clinical response measured by BASDAI compared with the rest of patients, although it did not reach statistical significance at 4 and 24 weeks (3.6±1.7 *vs*. 4.1±1.9 $p>0.050$) and (2±1.5 *vs*. 2.8±2.0 $p>0.050$), respectively.

Finally, quality of life significantly improved at 4 and 24 weeks (10.1±4.4 *vs*. 6.9±4.8 and 4.1±4 respectively, $p<0.001$). The degree of satisfaction and the willingness to continue etoricoxib (2.5±1.2 and 2.4±0.8 respectively) were reported as good at all study points.

Safety

Seven patients (12%) withdraw due to arterial hypertension (Fig. 1). Four of them had previously arterial hypertension that worsened after etoricoxib treatment. Only one patient presented a serious adverse event (an intracerebral hematoma) potentially related to etoricoxib treatment. This was a patient with a previous neurovascular malformation and arterial hypertension.

Discussion

In this four-week pragmatic open-label study, etoricoxib achieved a good clinical response in one third of patients; this effect was evident even in patients who were very active despite classical NSAID treatment and therefore met criteria for anti-TNF-α therapy. These data are consistent with those observed at the end of the extension study.

Our results confirm what it was previously published in a pilot study (20), and are in agreement with some other reports suggesting that etoricoxib could have a higher clinical effect in patients with active AS compared to classical NSAID (19). In contrast to the six week pilot study (20), the primary objective in our study was recorded at four weeks. There is consistent evidence supporting that a four week period is enough to assess the maximum effect of NSAID treatment (27, 28). On the other hand, the results observed at two weeks were clearly worse than those reported at four weeks, suggesting that the response at two weeks does not appear to predict late response to etoricoxib.

The mechanism of etoricoxib superiority compared to classical NSAID in AS patients has not been clearly established. However, the tolerability of etoricoxib at high doses (16), the power of its effect on symptoms at a daily dose of 90 mg (20), and probably the ease to comply with a full dose of treatment in clinical practice (one pill a day) due to the long half-life of etoricoxib may partially explain these results. Nevertheless, a specific effect of etoricoxib linked to its profile consisting of a cyclooxygenase-2 selective inhibition cannot be ruled out (29-31).

On the other hand, the results observed at four weeks were roughly maintained at six months, showing that around one third of patients had at that time a good clinical response that prevented the start of anti-TNF-α therapy. Although the period of time was not long, the impact of these results on disease costs cannot be overlooked, especially in our current economic situation. Additionally, the improvement of patients' health-related quality of life, along with the willingness to continue treatment, reinforces the fact that etoricoxib was a well-tolerated and acceptable treatment for these patients.

Table II. Changes in clinical variables from baseline*.

Variable	Study entry (n=57) Mean (SD)	4 weeks (n=53) Mean (SD)	Δ in units	Δ in %	24 weeks (n=23) Mean (SD)
BASDAI	6.0 (1.5)	3.8 (1.8)	-2.2	-62	2.6 (1.9)
Patient VAS	6.4 (1.9)	3.9 (2.4)	-2.4	-60	2.9 (2.4)
Physician VAS	6.2 (1.4)	3.2 (1.4)	-2.9	-52	2.6 (1.7)
Night back pain VAS	6.6 (2.1)	3.3 (2.3)	-2.6	-50	2.9 (2.3)
CRP (mg/L)	11.1 (13.0)	8.3 (10.0)	-2.0	-22	4.0 (3.0)
BASFI	5.0 (2.1)	3.5 (2.0)	-1.7	-34	2.2 (2.3)
ASQoL	10.1 (4.4)	6.9 (4.8)	-3.2	-32	4.1 (4.0)

*Improvements in clinical variables were statistically significant ($p<0.001$) at all study points except for CRP $p<0.050$ (from non-parametric tests) at all study points.
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; VAS: visual analogue scale; CRP: C-reactive protein; mg: milligram; L: litre; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQoL: Ankylosing Spondylitis Quality of Life.

Most patients showed a moderate or high disease activity at baseline and no one had inactive disease according to ASDAS-CRP. Around a quarter of patients was inactive or presented low disease activity at 4 weeks. ASDAS-CRP is a tool recently suggested by EULAR recommendations to monitor treatment in AS (15, 32). The ASDAS-CRP results with etoricoxib complement the response found in other more subjective clinical parameters and are of great interest given the relationship reported between ASDAS-CRP and axial structural damage measured by mSASS (33). Moreover, it has been described that patients with elevated acute phase reactants seem to benefit most from continuous treatment with NSAIDs, in terms of radiological progression (2).

Although most patients reported moderate-to-high clinical activity, mean CRP levels were slightly elevated and only half of patients presented high CRP levels at study entry, similar to previous reports. Limited data are available regarding the effect of NSAID on CRP. Some reports support a modest effect of classical NSAID on CRP (34). However, this issue remains unclear. Our data showed a progressive CRP decrease from baseline to the end of the study but it did not achieve statistical significance. Nevertheless, a third of the patients with good clinical response normalised CRP levels. Besides, patients with high CRP levels also showed a slightly better clinical response measured by BASDAI in all assessment points. Etoricoxib results presented in this study were in agreement with previous reports of AS patients under anti-TNF-α therapy, suggesting that CRP serum level is a potential predictor for treatment response (35).

Finally, etoricoxib appeared to be a quite safe therapy given that only 12% of patients had to withdraw from the study due to adverse events. In all cases the adverse events were related to arterial hypertension and in most cases arterial hypertension was already present. There was only one serious adverse event, an intracerebral hematoma, which appeared in a patient with a previous vascular brain malformation.

A number of limitations should be taken into account when interpreting the results of this paper. The lack of a control group makes difficult the interpretation of clinical data; it is open, therefore subject to placebo effect. However, the fact that AS diagnosis was well established, that only patients with high disease activity in spite of the use of classic NSAID were included, along with the consistent improvement in all clinical variables, including some objective variables such as ASDAS-C and CRP, support the efficacy of etoricoxib. It is true that we cannot rule out low compliance at baseline – and not truly refractory – and including low-compliant patients in the trial may have improved adherence to NSAID treatment and thus improved effect. However, these were patients ready for anti-TNF therapy, so that they would represent the typical refractory patient in practice. On the other hand, the pragmatic design of our study probably reflects clinical practice more precisely than a randomised clinical trial. Unfortunately, our results are not conclusive, probably because of the sample size. In addition, the study duration was relatively short. However, our data at six months support previous evidence suggesting that there is a similar proportion of NSAID responders at 6 weeks and at 1 year (14, 16). We chose a 6-months extension because we consider that this period could reflect the impact of the etoricoxib on clinical practice, including economic issues. The lack of spinal imaging (x-ray or MRI) limited the evaluation of NSAID on the natural history of AS. However, the study period was too short to evaluate changes in x-ray examination. Unfortunately, we did not perform a MRI study of these patients; however, the effect of NSAID on bone marrow oedema evaluated by MRI seems to be very weak (20) and on the other hand, it is unclear whether MRI findings predict treatment response (36), or future ankylosis (37, 38). Thus, MRI was not included in the core set of measures for monitoring response in AS patients.

In conclusion, this pragmatic study shows that etoricoxib provided a relevant clinical improvement in nearly a third of patients with AS refractory to classical NSAID. These results were maintained up to six months, suggesting a significant impact of etoricoxib on the management of these patients. Special care should be required when deciding to start anti-TNF-α therapy and it seems reasonable to keep in mind these results, although more experience and further investigation are necessary to clear up this issue.

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