The Efficacy of Cyclooxygenase-2 Inhibition by Etoricoxib and Naproxen on the Axial Manifestations of Ankylosing Spondylitis in the Presence of Peripheral Arthritis

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The Efficacy of Cyclooxygenase-2 Inhibition by Etoricoxib and Naproxen on the Axial Manifestations of Ankylosing Spondylitis in the Presence of Peripheral Arthritis

Full-length Report
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Key words: ankylosing spondylitis, NSAIDs, efficacy, peripheral arthritis, etoricoxib

Running foot line: NSAIDs efficacy in AS

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Abstract

Objective: We evaluated the combined efficacy of selective and non-selective cyclooxygenase-2 (COX-2) inhibition on the axial manifestations of ankylosing spondylitis in the presence or absence of chronic peripheral arthritis.

Methods: This was a post-hoc subgroup analysis of a 6-week, randomized, double-blind, placebo-controlled trial. A total of 387 patients with active axial AS were randomized to receive etoricoxib 90mg or 120mg q.d., naproxen 500mg b.i.d., or placebo. Randomization was stratified by the presence or absence of chronic peripheral arthritis. The primary outcome measure for this analysis consisted of time-weighted average change from baseline of spine pain intensity. Efficacy data from the 3 active treatment groups (the NSAID/COX-2 inhibitor group) were combined to improve precision. An ANCOVA model was used to evaluate the effect of peripheral disease on treatment response.

Results: 93 patients were allocated to receive placebo and 294 to active treatment (naproxen or etoricoxib). The combined NSAID/COX-2 inhibitor group demonstrated a significant treatment response versus placebo for all efficacy measures both in patients with and without peripheral arthritis. However there was a significantly greater difference in mean patient assessment of spine pain between active and placebo treatments in patients without versus those with peripheral arthritis (p=0.005: -32.5 mm vs. -17.0 mm, respectively). Although not statistically significant, similar differences were seen for other endpoints.

Conclusion: NSAIDs and COX-2 inhibitors have a clinically relevant symptomatic effect on axial AS irrespective of the presence of peripheral arthritis. However, in this exploratory analysis spinal improvement appears greater in patients without peripheral disease.
The group of diseases collectively labeled the spondyloarthropathies share different rheumatic manifestations; spinal symptoms predominate, but extraspinal joint disease (peripheral arthritis) and enthesiopathic lesions also occur [1]. Ankylosing spondylitis (AS) is the prototype of this group of interrelated disorders. Axial skeletal disease with sacroiliitis and spinal involvement is the hallmark of AS. Asymmetric peripheral arthritis is present in about 20-40% of AS patients. The objectives for treatment of the axial involvement of AS are to reduce and/or prevent the deleterious clinical progression of the disease, which is characterized by inflammation and increasing ankylosis leading to abnormal posture and decreased mobility.

Nonsteroidal anti-inflammatory drugs (NSAIDs) acting via inhibition of COX-2 have been the cornerstone of treatment for patients with AS since the introduction of phenylbutazone [2]. Most of the clinical trials involving NSAIDs clearly demonstrate substantial, quick relief of pain and inflammation. Because of this, the diagnosis of AS includes a therapeutic response to NSAID therapy within 48 hours or rapid relapse following cessation of therapy [3]. However, it is unclear whether the therapeutic response to NSAIDs entails the axial symptoms, the peripheral arthritis and/or the enthesiopathic features. Nonselective NSAIDs have been shown to be efficacious in the treatment of the signs and symptoms of axial disease. However, clinical data from patients with peripheral arthritis is limited. Despite the lack of data-driven information most clinical trials evaluating the symptomatic effect of NSAIDs in axial involvement of AS have excluded patients suffering from concomitant peripheral arthritis. This exclusion was essentially based on the judgment of clinical experts that the clinical presentation comprising peripheral articular involvement might interfere with the treatment effect of NSAIDs on the axial symptoms. From our personal clinical experience, prior to this post-hoc analysis, we also hypothesized that concomitant peripheral arthritis may influence the efficacy of COX-2 inhibition on the axial skeleton. However, this hypothesis has never been explored.

The successful relief of the pain and symptoms of AS with NSAIDs and COX-2 selective inhibitors strongly suggests a role for COX-2 inhibitors for the treatment of the disease. Etoricoxib, a COX-2 selective inhibitor, effectively relieves the pain and symptoms associated with rheumatoid arthritis, osteoarthritis, chronic low back pain, and gout [4]. We recently conducted a two-part 52-week controlled clinical trial in patients with AS, comparing the efficacy of daily etoricoxib 90 or 120 mg with twice daily naproxen 500 mg, and placebo on the axial and peripheral manifestations of the disease [5]. In that study, etoricoxib provided clinically superior relief from the signs and symptoms of AS compared to both naproxen and placebo and naproxen was superior to placebo. Since in that trial, treatment assignment was stratified for the presence or absence of chronic peripheral arthritis or history of peripheral arthritis, in this analysis we took the opportunity to evaluate whether or not the treatment effect on the axial skeleton was different in the presence or absence of peripheral arthritis.

The aim of this post-hoc, hypothesis generating, analysis was to explore the axial treatment response resulting from etoricoxib- and naproxen-mediated COX-2 inhibition in AS patients with isolated axial disease, compared to those who also had peripheral arthritis.
Patients and Methods

Patients. All patients provided their written informed consent prior to entering the study. The eligibility criteria for this study have been previously described [5]. All patients were required to have radiographic evidence of sacroiliitis as defined in the Modified New York criteria [6] for the classification of AS. Inclusion criteria included: regular NSAID intake defined as at least 25 of the previous 30 days; NSAID or COX-2 inhibitor-specific washout period of 3-20 days before the baseline visit; a flare of the disease at baseline, defined by pain \( \geq 40 \) mm (on a 100-mm visual analog scale, VAS), and by an increase in pain of at least 30% and minimum 12 mm compared with the screening visit; for patients taking disease-modifying drugs (DMARDs), a stable dose for at least 3 months; and for patients on low-dose aspirin, a stable aspirin dose for at least 14 days.

Patients with acute peripheral disease, defined by the onset within 4 weeks prior to the study of active (painful or swollen) peripheral arthritis (except hip and shoulder), were excluded from enrollment in the study. Patients with chronic peripheral arthritis were permitted to enroll in the study, provided that the spine was the primary source of pain. Patients were classified as having “chronic peripheral arthritis” if they had painful or swollen peripheral arthritis > 4 weeks duration, or a history of peripheral arthritis. History of peripheral arthritis was an anamnestic element which was recorded at study inclusion by the investigator, based on perusal of the patient’s full medical chart and on patient recall. Patients with severe concomitant illness or with active inflammatory bowel disease were ineligible. Patients who had received corticosteroids or misoprostol during the previous month were also ineligible for the study.

Study design.

The study was a multicenter, international 2-part, randomized, double-blind, parallel-group, placebo- and active-comparator controlled study in patients with AS, conducted with in-house blinding, to evaluate the safety, tolerability and efficacy of etoricoxib 90mg and 120mg once daily versus naproxen 500mg twice daily and placebo [5]. Treatment assignment was stratified by the absence or presence of chronic peripheral arthritis. The local ethics committee of each study center approved this clinical trial. The work presented here is an analysis of the 6-week placebo-controlled portion of the study. Since etoricoxib and naproxen both exert their analgesic and anti-inflammatory efficacy via inhibition of COX-2, we combined data from both of the active treatment groups to increase sample size and precision for a subgroup analysis in patients with and without peripheral arthritis.

Study drugs.

Patients were randomly assigned (1:1:1:1) to receive placebo, etoricoxib 90mg or 120mg daily, or naproxen 500mg twice daily. Acetaminophen (500mg per tablet, maximum 6 tablets per day) was used as a rescue medication during the study, when needed. Corticosteroids and analgesics other than the assigned NSAID (naproxen) or COX-2 inhibitor (etoricoxib) were not allowed.
Clinical Endpoints Used for Analyses in this Report. This post-hoc subgroup analysis based on the presence or absence of chronic peripheral arthritis was performed on the following endpoints:

- the pre-specified primary endpoint for this analysis: Patient Assessment of Spine Pain (Bath Ankylosing Spondylitis Disease Activity Index, BASDAI question 2);
- the pre-specified co-primary endpoints for the efficacy analysis (main analysis of the trial [5]): Patient Global Assessment of Disease Activity; Bath Ankylosing Spondylitis Functional Index (BASFI);
- post-hoc endpoints: Patient Assessment of Peripheral Pain (BASDAI Question 3); BASDAI stiffness (average of BASDAI Questions 5 and 6); and BASDAI enthesopathy (Question 4) [7,8]. The ASAS20 responders were also determined post-hoc: percent of patients experiencing symptomatic improvement of ≥20% and absolute improvement of ≥10 units (on a scale of 1-100) in ≥3 of four outcome domains and no worsening by the same amount in the fourth domain (as recommended by the Ankylosing Spondylitis Working Group [9]). The four domains are: patient global assessment, pain, function, and inflammation (morning stiffness). The ASAS20 criteria became available only after the primary study started and were therefore a post-hoc endpoint.

Statistical Analyses. These analyses combined patients treated with etoricoxib and naproxen into one active treatment group to maximize precision. Although superior efficacy was observed for etoricoxib over naproxen, effect sizes for patients with, compared to patients without chronic peripheral arthritis, were consistent for all active treatment groups (e.g., Patient Assessment of Spine Pain, treatment effect comparing axial-peripheral: etoricoxib 90 mg = -7.6 mm; etoricoxib 120 mg = -9.0 mm; and naproxen 1000 mg = -7.1 mm). Thus it was considered that the best estimate of the difference in response in patients with and without peripheral arthritis would be provided by pooling the groups. In addition, the mechanism of the analgesic and anti-inflammatory actions of both agents is via inhibition of COX-2 and both demonstrated statistically significant improvements in efficacy versus placebo.

Analyses were based on the time-weighted average change from baseline for all observations across the 6-week treatment period. All patients who provided a measure at baseline and at least one measurement at a post-baseline observation time were included in the analyses. Analysis of covariance (ANCOVA) was used to accomplish the subgroup analyses. Categorical factors in the ANCOVA model included treatment (COX-2 inhibitor group or placebo), peripheral arthritis (history or presence, or absence), and the interaction; and the baseline measure was included as a continuous covariate. The consistency of the treatment effects across subgroups of patients with and without chronic peripheral arthritis was assessed with the ANCOVA f-test for the interaction effect. Least squares mean change from baseline and the associated difference between the active group and placebo were computed along with 95% confidence intervals (CI). Since this was a hypothesis-generating analysis, testing for multiplicity was not performed.
Results. Baseline patient characteristics are presented in table 1. Forty percent of the patients experienced chronic peripheral arthritis. In the group of patients with peripheral arthritis: 94 (60.7%) had a prior history and 58 (37.4%) had currently active arthritis of the hand, foot, elbow, ankle, and/or knee. Prior or current arthritis was reported at other sites by 3 (1.9%) of the patients in the peripheral arthritis group. Two of these patients had arthritis of the hip and/or shoulder. Inclusion of these two patients in the analysis did not change the results obtained. The patients were primarily male, under the age of 50, experienced low back pain, had limitations of the lumbar spine and chest expansion, and 37% had grade 4 AS with complete ankylosis of the sacro-iliac joints [6]. The two groups appeared to be well balanced except for a higher percentage of concomitant DMARD and prior corticosteroid use in the group with peripheral arthritis.

Table 1. Patient demographics and accounting

<table>
<thead>
<tr>
<th></th>
<th>Peripheral Arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YES N=155</td>
</tr>
<tr>
<td>Gender: male [n (%)]</td>
<td>115 (74.2)</td>
</tr>
<tr>
<td>Age (yrs): mean (SD)</td>
<td>43.8 (13.9)</td>
</tr>
<tr>
<td>Age (yrs): range</td>
<td>18 to 78</td>
</tr>
<tr>
<td>Low Back Pain at Rest [n (%)]</td>
<td>152 (98.1)</td>
</tr>
<tr>
<td>Limitation of Lumbar Spinea</td>
<td>140 (90.3)</td>
</tr>
<tr>
<td>Limitation of Chest Expansionb [n (%)]</td>
<td>103 (66.5)</td>
</tr>
<tr>
<td>Sacroiliitis Grade 4 [n (%)]</td>
<td>53 (34.2)</td>
</tr>
<tr>
<td>Prior DMARD Use [n (%)]</td>
<td>77 (49.7)</td>
</tr>
<tr>
<td>Prior Corticosteroid Use [n (%)]</td>
<td>54 (34.8)</td>
</tr>
<tr>
<td>Concomitant DMARD Use [n (%)]</td>
<td>49 (31.6)</td>
</tr>
</tbody>
</table>

a. Limitation of motion of the lumbar spine in both the sagittal and frontal planes.

b. Limitation of chest expansion relative to normal values corrected for age and sex.
A significant treatment by peripheral arthritis strata interaction was only detected for patients’ assessment of spine pain (table 2). Specifically, there was a greater difference in spinal pain response between the active and placebo groups in AS patients without (-32.5 mm; 95% CI: -39.2, -25.7) relative to AS patients with chronic peripheral arthritis (-17.0 mm; 95% CI: -25.3, -8.7).

Table 2. Subgroup Analysis of Patient Assessment of Spine Pain (100 mm VAS) Based on Presence of Peripheral Arthritis or History of Peripheral arthritis

<table>
<thead>
<tr>
<th>Peripheral Arthritis Subgroup</th>
<th>Placebo</th>
<th>Active Treatment</th>
<th>Difference in LS Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>LS Mean (SE)</td>
<td>N</td>
<td>LS Mean (SE)</td>
</tr>
<tr>
<td>Chronic arthritis</td>
<td>14</td>
<td>-15.3 (6.0)</td>
<td>44</td>
</tr>
<tr>
<td>History of arthritis</td>
<td>23</td>
<td>-18.8 (4.6)</td>
<td>73</td>
</tr>
<tr>
<td>None</td>
<td>56</td>
<td>-10.0 (3.0)</td>
<td>175</td>
</tr>
</tbody>
</table>

Treatment by peripheral arthritis subgroup interaction test p-value = 0.016

Similar differences between patients with and without peripheral arthritis were also seen for other endpoints including ASAS20, but these did not reach statistical significance (table 3). These differences were mainly related to a lower efficacy of NSAIDs in patients with peripheral arthritis, rather than a higher placebo effect (table 3). Statistically significant symptomatic improvement following active treatment was observed for all primary and post-hoc endpoints (table 3) including the ASAS20 responder criteria for symptomatic improvement (Figure 1). Except for patients’ assessment of spine pain, the improvement from baseline in the placebo group was greatest in the group without peripheral arthritis. Inclusion of prior or current use of DMARDs in the interaction model as covariates provided a similar significant treatment by peripheral arthritis strata interaction for patients’ assessment of spine pain.
**Table 3. Analysis of AS endpoints stratified by presence/history or absence of chronic peripheral arthritis**

<table>
<thead>
<tr>
<th>Peripheral Arthritis</th>
<th>Treatment</th>
<th>N</th>
<th>Baselineᵃ</th>
<th>Change From Baseline</th>
<th>Difference (95% CI)</th>
<th>LS Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence</td>
<td>Placebo</td>
<td>37</td>
<td>78.7</td>
<td>-17.5 (-24.7, -10.3)</td>
<td>-17.0* (-25.3, -8.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Active</td>
<td>117</td>
<td>73.6</td>
<td>-34.5 (-38.6, -30.4)</td>
<td>-17.0* (-25.3, -8.7)</td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>Placebo</td>
<td>56</td>
<td>76.2</td>
<td>-10.0 (-15.9, -4.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Active</td>
<td>175</td>
<td>77.7</td>
<td>-42.5 (-45.8, -39.2)</td>
<td>-32.5* (-39.2, -25.7)</td>
<td></td>
</tr>
</tbody>
</table>

**Patient Assessment of Spine Pain (VAS)**

Treatment by Strata Interaction Test p-value= 0.005

| Presence    | Placebo   | 37  | 61.8      | 0.9 (-5.9, 7.6) |                     |
| Absence     | Placebo   | 56  | 45.4      | -5.5 (-11.0, -0.1) |                     |
| Absence     | Active    | 175 | 43.5      | -26.6 (-29.7, -23.5) | -21.1* (-27.4, -14.8) |

**Patient Assessment of Peripheral Pain - BASDAI Question #3 (VAS)**

Treatment by Strata Interaction Test p-value= 0.45

| Presence    | Placebo   | 37  | 61.8      | 0.9 (-5.9, 7.6) |                     |
| Absence     | Placebo   | 56  | 45.4      | -5.5 (-11.0, -0.1) |                     |
| Absence     | Active    | 175 | 43.5      | -26.6 (-29.7, -23.5) | -21.1* (-27.4, -14.8) |

**Patient Assessment of Enthesopathy - BASDAI Question #4 (VAS)**

Treatment by Strata Interaction Test p-value= 0.29

| Presence    | Placebo   | 37  | 66.5      | 3.3 (-10.0, 3.5) |                     |
| Absence     | Placebo   | 56  | 62.8      | -4.3 (-9.7, 1.2)  |                     |
| Absence     | Active    | 175 | 63.4      | -28.0 (-31.1, -24.9) | -23.7* (-30.0, -17.5) |

**Patient Global Assessment of Disease Activity (VAS)**

Treatment by Strata Interaction Test p-value= 0.32

| Presence    | Placebo   | 37  | 55.2      | 3.5 (-9.2, 2.3)  |                     |
| Absence     | Placebo   | 56  | 53.4      | -1.1 (-9.8, -0.4) |                     |
| Absence     | Active    | 175 | 53.7      | -20.3 (-22.9, -17.6) | -15.2* (-20.6, -9.8) |

**Bath Ankylosing Spondylitis Functional Index (VAS)**

Treatment by Strata Interaction Test p-value= 0.39

| Presence    | Placebo   | 37  | 61.8      | 5.7 (-12.4, 1.0)  |                     |
| Absence     | Placebo   | 56  | 65.0      | -6.2 (-11.6, -0.7) |                     |
| Absence     | Active    | 175 | 62.6      | -28.7 (-31.8, -25.6) | -22.5* (-28.8, -16.2) |

**Morning Stiffness - Mean of BASDAI Questions 4 & 5 (VAS)**

Treatment by Strata Interaction Test p-value= 0.45

| Presence    | Placebo   | 37  | 61.8      | 5.7 (-12.4, 1.0)  |                     |
| Absence     | Placebo   | 56  | 65.0      | -6.2 (-11.6, -0.7) |                     |
| Absence     | Active    | 175 | 62.6      | -28.7 (-31.8, -25.6) | -22.5* (-28.8, -16.2) |

ᵃ. Mean ± SD; * Difference from placebo is statistically significant at p < 0.05
Discussion. Most clinical studies of patients with AS have excluded individuals with a history of peripheral arthritis. In this study we enrolled AS patients with and without peripheral disease provided that the spine was the primary source of pain. We used validated clinical response criteria [9] to demonstrate that inhibition of COX-2, in the combined etoricoxib and naproxen groups, provided significant clinical efficacy in AS patients with and without peripheral arthritis. The treatment responses observed across the clinical endpoints for the combined active treatment group compared to placebo treatment are in agreement with those observed in other trials of NSAIDs in patients with AS [9]. However, the magnitude of these responses was larger in patients without chronic peripheral arthritis or a history of peripheral arthritis. Although a significant difference in treatment effect among those with versus those without peripheral arthritis was only observed for the primary endpoint of spinal pain, other endpoints demonstrated qualitatively similar differences suggesting an overall difference in response between the two patient subgroups. Furthermore, it is not surprising that the differential effect should be clearest for spinal pain since the other endpoints are global AS endpoints.

One explanation could be that in patients with chronic peripheral arthritis, the painful sensation of the peripheral joints interferes with the spinal pain. However the results are similar for patients with chronic arthritis and with a history of arthritis.

The pathophysiologic mechanisms responsible for the difference in treatment response between patients with and without peripheral arthritis have yet to be elucidated. These differences could reflect quantitative differences in the degree of inflammation, qualitative differences in the production of biochemical mediators which drive the inflammatory processes in these two subgroups, or perceptual differences in the level and extent of pain. To date, neither radiographic nor pathologic studies have conclusively identified differences in the axial skeletal manifestations of disease in patients with and without peripheral arthritis that might explain our findings. It is known that patients both with and without peripheral arthritis have enthesopathies and both patient subgroups suffer from synovitis of their synarthrodial joints. It is also known that COX-2, a rate-limiting enzyme in the prostaglandin biosynthetic pathway, is highly expressed in the synovium of patients with AS. Moreover, in patients with AS the level of COX-2 in synovial tissues appears to be proportional to the severity of disease [10]. To-date, studies examining the relative expression of prostaglandins in peripheral versus axial joints or in patients with peripheral versus those without peripheral arthritis have not been performed.

Of interest, although not measured in this study, historic data suggest that circulating levels of acute phase reactants are higher in AS patients with peripheral arthritis [11,12], than in those without. These could reflect quantitative differences in the level of inflammation in these patients, or qualitative differences in the production of cytokines (or other inflammatory mediators) that drive this inflammation. Since it is known that NSAIDs and COX-2 selective inhibitors have little to no effect on acute phase reactants, the possibility exists that there are additional mediators of inflammation in patients with peripheral arthritis that are not well attenuated by cyclooxygenase inhibition.
Also of interest in the interpretation of these exploratory findings is the relative contribution of enthesopathy versus synovitis in the manifestation of spinal pain. Both are inflammatory processes but one might be more driven by prostanoids than the other. This field is worthy of further study.

In conclusion, both NSAIDs and COX-2 selective inhibitors offer an effective treatment for AS patients with and without peripheral arthritis but the relative treatment effects appear to be greater in those without a history of arthritis or chronic peripheral arthritis. The greater treatment effects in patients without peripheral arthritis suggest that they may suffer from different disease processes which are more NSAID responsive than those in patients with peripheral arthritis. It also suggests that the pathophysiology of AS warrants further study, particularly in regard to disease mediators and their relative contribution in distinct patient populations.

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Figure 1. Percent of AS patients with and without peripheral arthritis who demonstrated symptomatic improvement based on ASAS 20 criteria. Dark bars (placebo group); hatched bars (active groups). Note that the treatment by strata interaction did not reach significance for the ASAS20 endpoint (p=0.52).
References

Chronic Peripheral Arthritis

Present

Absent

ASAS 20 responders (%)

$\text{Placebo}$

$\text{Active}$

$n=37$ $n=118$

$n=56$ $n=176$

$p = 0.001$

$p < 0.001$
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