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ORIGINAL ARTICLE

Clinical Efficacy of Celecoxib Compared to Acetaminophen in Chronic Nonspecific Low Back Pain: Results of a Randomized Controlled Trial

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Objective. **In this randomized controlled trial, we compared the effect of celecoxib and acetaminophen on pain and magnetic resonance imaging (MRI) scores in patients with chronic nonspecific low back pain.**

Methods. **A total of 50 patients with chronic nonspecific low back pain were blindly randomized into 2 groups treated with celecoxib (200 mg twice daily) or acetaminophen (500 mg twice daily). Outcome measures included total back pain, nocturnal back pain, Oswestry Disability Index (ODI) scores, the Short Form 36 health survey to assess physical and mental status, and patient global assessment. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index, and Bath Ankylosing Spondylitis Metrology Index scores were also assessed before and after the therapy. The Spondyloarthritis Research Consortium of Canada scoring method was used to evaluate spinal MRI changes.**

Results. **Celecoxib showed a superior effect on total back pain, ODI, BASDAI, nocturnal back pain, and patient global assessment, compared to acetaminophen ($P < 0.05$). The number of patients with a significant change in back pain scales was higher in the celecoxib arm (ODI 34.8% versus 4.5%, nocturnal back pain 41.7% versus 9.1%, total back pain 33.3% versus 9.1%, and BASDAI 30.4% versus 9.1%; $P < 0.01$ for all). The responsiveness to celecoxib, calculated by Guyatt's Responsiveness Index, was 1.62, 1.28, 1.27, and 0.58 for the ODI, total back pain, BASDAI, and nocturnal back pain, respectively. The MRI scores for sacroiliac joints and spine showed no significant change with either treatment when compared with baseline values ($P > 0.05$).**

Conclusion. **There was superior efficacy of celecoxib compared with acetaminophen in chronic nonspecific low back pain. Inflammatory lesions of sacroiliac joints and spine are commonly seen in nonspecific low back pain, but these lesions did not change with either celecoxib or acetaminophen treatments and were not associated with clinical response to either agent.**

INTRODUCTION

Low back pain (LBP) is a common problem at the population level that can interfere with activities of daily living and can impose significant disability (1,2). It may originate from many spinal structures, including muscles, fascia, ligaments, facet joints, vertebral periosteum, spinal nerve roots or blood vessels (3). More than 85% of patients seeing a primary care provider have nonspecific low back pain (NSLBP), which refers to a condition that cannot be reliably attributed to a specific disease or spinal abnormality. Musculoligamentous injuries and age-related degenerative processes in the intervertebral disks and facet joints are the most common causes of NSLBP (4). The prevalence

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Significance & Innovations

- Celecoxib (200 mg twice daily) showed greater efficacy on chronic nonspecific low back pain scales and disability index compared to acetaminophen (500 mg twice daily).
- Inflammatory lesions of sacroiliac joints and spine did not change after celecoxib or acetaminophen therapy.
- Patients who were treated with celecoxib had 4 times greater chance than the acetaminophen-treated group to reach the therapeutic pain control target.

and high cost of this problem are expected to keep rising over the coming years (5,6). More than half the population are expected to experience symptoms of LBP at least once in their life (7). Fortunately, about 90% of the cases will demonstrate a benign course. However, some patients will continue experiencing LBP and proceed to a chronic state (more than 3 months) (8).

An ongoing clinical challenge is determining the primary source of the spinal pain. Differentiating between chronic NSLBP, which accounts for nearly 90% of chronic LBP, and inflammatory back pain plays a crucial part in designing the therapeutic plan for patients. In addition to the medical history and clinical examination, magnetic resonance imaging (MRI) has recently become an important part of diagnosis and clinical classification, especially with the added advantage of being a noninvasive procedure using low-radiation exposure. MRI-defined inflammatory lesions have been used to differentiate between axial spondyloarthritis (SpA) and NSLBP, but the frequency of inflammatory lesions in chronic NSLBP remains unresolved (9).

Many pharmacologic and nonpharmacologic therapeutic options have been used for NSLBP (10). Nonsteroidal antiinflammatory drugs (NSAIDs) and analgesic agents are widely prescribed by physicians. They are also frequently used by patients as over-the-counter medications. However, analgesic agents such as acetaminophen are also widely used for NSLBP. The biggest challenge for the health provider is to establish enough evidence to preferentially select one class over the other. Most current guidelines recommend both NSAIDS and analgesics as therapeutic options (11). Selective cyclooxygenase 2 (COX-2) inhibiting NSAIDs (coxibs) have become available as an alternative to traditional NSAIDs. The main advantage of these formulations is lower risk of gastrointestinal adverse events as compared to nonselective COX-2 inhibitors. Currently, there are a limited number of randomized clinical trials that have evaluated the efficacy of coxibs in chronic NSLBP (12), and to our knowledge, the efficacy of celecoxib in this population has not been studied before. In this article, we provide the results of a randomized, double-blind study to evaluate the effect of celecoxib in comparison to acetaminophen in chronic NSLBP. In addition, we investigated the effect of treatment on inflammatory lesions in the spine and sacroiliac joints (SIJs), detected by MRI.

PATIENTS AND METHODS

Patients and recruitment. Patients were consecutively recruited from a specific back pain clinic in a tertiary hospital according to the following criteria: LBP (from T12 to buttocks) lasting >3 months, visual analog pain scale score ≥4 of 10 in the past week, ages ≥18 years, nondiagnostic SIJs on pelvic radiograph, normal erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level, and a willingness to take the trial medication for 4 weeks.

Patients were excluded if they had: surgery for LBP within 6 months of screening; LBP accompanied by sciatica; spondylolysis, spondylolisthesis, or spinal stenosis; inflammatory back pain or clinical or radiographic evidence of SpA; contraindication or known adverse effect for celecoxib or acetaminophen; unwillingness to undergo an MRI scan; or a history of mental, systemic, cardiac, renal, or hepatic diseases. All patients received instructions about the study procedures and medication. The study was compliant with the Declaration of Helsinki, and was approved by the hospital research ethics board at the participating institution. All study participants provided written informed consent.

Study details. In this double-blind, randomized, controlled trial, the main design features were washout, baseline measurements, randomization, intervention (acetaminophen or celecoxib), and effect measurements. A flowchart describing the study design is shown in Figure 1. Fifty patients with chronic NSLBP took part in the study. They were blindly randomized at an allocation ratio of 1:1 to receive to celecoxib (200 mg twice daily, n = 25) or acetaminophen (500 mg twice daily, n = 25) for 4 weeks. During the washout period (14 days prior to day 0), subjects taking NSAIDs were asked to discontinue their medications. Randomization was done by a simple randomization approach for 1 of the 2 conditions (acetaminophen or celecoxib). Immediately after baseline assessment (day 0), the primary investigator (RDI) gave the patient a numbered medication box according to randomization scheme. Patients who missed more than 3 consecutive days of treatment in 4 weeks of the study (noncompliant) were withdrawn from the trial.

Patient evaluation. To assess the pain severity before and after the course of treatment, 2 scales were used (total back pain [TBP] and nocturnal back pain [NBP]), which were scored on a 0–10 numerical rating scale completed by the patient. A patient global assessment was also included. The Oswestry Disability Index (ODI) was used to assess the degree of disability and to evaluate quality of life before and after the therapy (13). The Short Form 36 (SF-36) health survey mental component summary score and the physical component summary score were used to assess the physical and mental status of patients before and after the course of therapy (14). While the Bath indices are commonly applied in inflammatory back pain studies, we chose to include these in the outcome measures as a comparator. Thus, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the Bath Ankylosing Spondylitis Functional Index (BASFI), and the Bath Ankylosing Spondylitis Metrology Index (BASMI) were also assessed before and after the therapy (15–17). At least 50% reduction in back pain scale scores

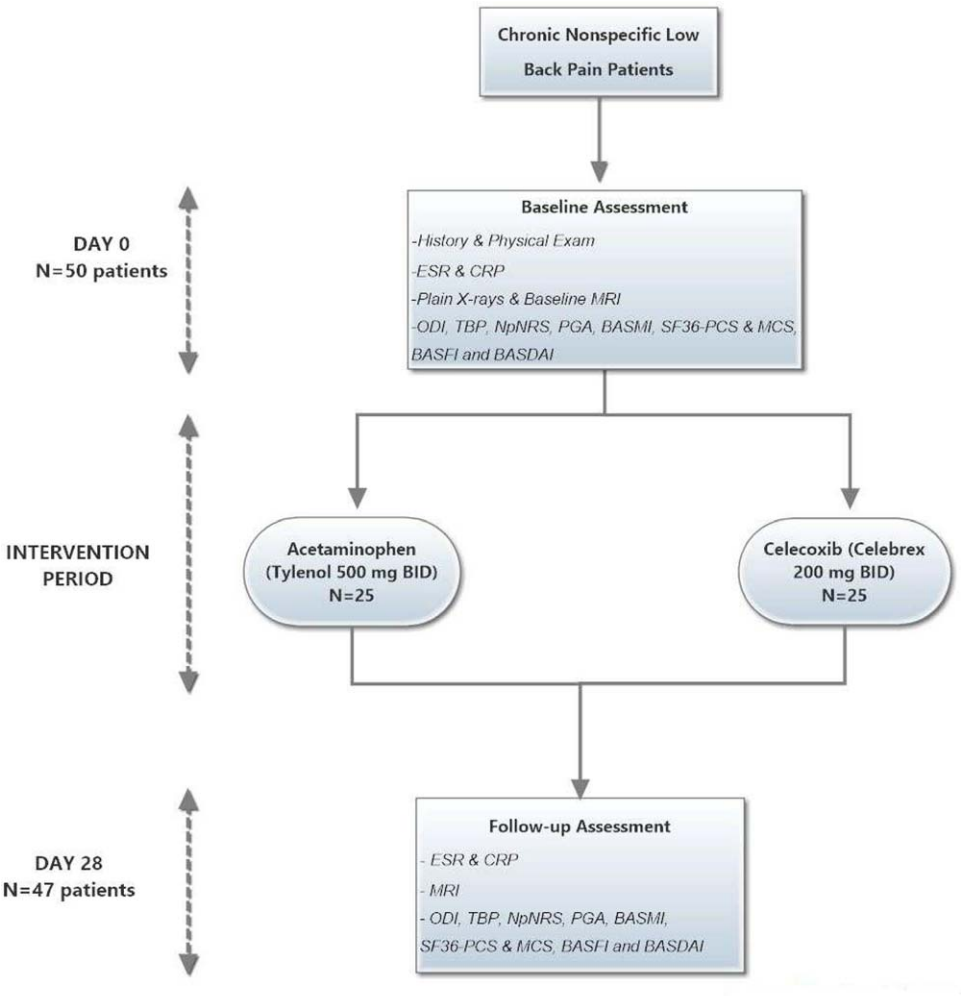

Figure 1. Study design. ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; MRI = magnetic resonance imaging; ODI = Oswestry Disability Index; TBP = total back pain; NpNRS = nocturnal back pain numerical rating score; PGA = patient global assessment; BASMI = Bath Ankylosing Spondylitis Metrology Index; SF-36 = Short Form 36 health survey; PCS = physical component summary; MCS = mental component summary; BASFI = Bath Ankylosing Spondylitis Functional Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BID = twice daily.

(TBP, NBP, ODI, and BASDAI) was considered a significant improvement.

The treatment effect size was determined by using the Guyatt Responsiveness Index (GRI), which was calculated for each back pain scale as the ratio of mean change of celecoxib group divided by the SD of the change of patients treated with acetaminophen. According to that formula, a GRI $\geq$0.8 was considered a large effect (18).

Participants' blood was drawn to record baseline and followup readings for inflammatory markers (CRP level and ESR). MRI of the SIJs and spine was performed at baseline and day 28. For evaluation of SIJs, Spondyloarthritis Research Consortium of Canada (SPARCC) (19) and Assessment of Spondyloarthritis international Society (ASAS)/Outcome Measures in Rheumatology (OMERACT) (20) criteria sets were used. Images of the spine were scored by using the SPARCC method (21). According to that protocol, only abnormalities on the STIR sequence were scored, and disc lesions were not counted (21).

Scorings were done independently by 2 central readers (IS and DS) who were blinded with regard to time point and treatment. Discordant cases were settled through consensus. The mean scores from the 2 readers were used for statistical analysis. For SPARCC scores, we used the proposed cutoff criteria $\geq$2 for positive spine and SIJ MRI results (22).

Statistical analysis. The Kolmogorov-Smirnov normality test was used to determine the distribution pattern of the variables. For continuous variables, results were presented as mean $\pm$ SD or median (minimum, maximum) values. Nominal and ordinal data were expressed as percentages. For comparison between 2 dependent groups (pre- and post-treatment periods), the paired sample *t*-test and McNemar's test were used. Fisher's exact test was performed for the comparison of categorical variables. Pre- and post-treatment difference (Δ change) comparisons between acetaminophen and celecoxib groups were made by Mann-Whitney U test. Correlation between the variables was done by using Pearson's

Table 1. Comparison of baseline characteristics of the treatment groups*

	Acetaminophen (n = 25)	Celecoxib (n = 25)	*P*
Age, years	37.2 ± 10.2	43.4 ± 11.2	0.13
Men, no. (%)	14 (56)	12 (48)	0.78
CRP, mg/liter	2.13 ± 2.8	2.12 ± 2.2	0.99
ESR, mm/hour	7.7 ± 9.1	5 ± 4.1	0.19
TBP	6.1 ± 1.8	6.5 ± 1.7	0.42
ODI	20.2 ± 8.4	20.4 ± 8.1	0.92
NBP	4.8 ± 2.3	4.7 ± 2.3	0.9
PGA	5 ± 1.8	4.7 ± 2.8	0.72
BASMI	1.6 ± 1.2	1.4 ± 1.4	0.58
BASDAI	4.7 ± 1.9	4.6 ± 2	0.92
BASFI	4.2 ± 4.3	4.2 ± 4.4	0.99
SF-36 PCS	37.9 ± 10.9	39.5 ± 9.2	0.59
SF-36 MCS	47.5 ± 9.8	44.7 ± 11.6	0.36
SPARCC spine	3.3 ± 4.5	5.5 ± 6.7	0.17
SPARCC SIJ	1.4 ± 1.8	0.9 ± 1.6	0.29
ASAS SIJ, %	20	20	1

* Values are the mean ± SD, unless indicated otherwise. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; TBP = total back pain; ODI = Oswestry Disability Index; NBP = nocturnal back pain numerical rating score; PGA = patient global assessment; BASMI = Bath Ankylosing Spondylitis Metrology Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; SF-36 = Short Form 36 health survey; PCS = physical component summary; MCS = mental component summary; SPARCC = Spondyloarthritis Research Consortium of Canada; SIJ = sacroiliac joint; ASAS = Assessment of Spondyloarthritis international Society.

test. Single measures intraclass correlation coefficient values and kappa statistic were used to analyze the reliability. A double-tailed *P* value of less than 0.05 was considered statistically significant. The statistical analysis was carried out by using SPSS software, version 22.

RESULTS

Baseline characteristics of the treatment groups. Initially there was a total of 50 patients in the study (26 men and 24 women) with a mean ± SD age of 41.1 ± 10.9 years. Baseline comparison of acetaminophen and celecoxib groups showed that age, sex distribution, acute-phase protein levels (CRP level and ESR), back pain scales (ODI, TBP, NBP, and BASDAI), patient global assessment, functional indices (BASFI), spinal mobility assessments (BASMI), quality-of-life measures (SF-36 mental component summary and physical component summary), and spinal MRI assessments (SPARCC spine and SIJ scores) were similar between the treatment groups ($P > 0.05$) (Table 1). Baseline SPARCC spine and SIJ scores did not show any correlation with baseline values of CRP level, ESR, BASDAI, BASFI, BASMI, ODI, TBP, and NBP scales ($P > 0.05$).

Treatment effect on study parameters. One female patient in the celecoxib arm was lost to followup and another female patient in the acetaminophen arm was withdrawn from the study due to knee injury. There was also one female patient in the acetaminophen group whose HLA–B27 typing was positive and SIJ and spine MRI scores were ≥2. After re-evaluation, this patient was diagnosed as having axial SpA and removed from the analysis. A total of 47 patients completed the study.

Table 2. Clinical and laboratory parameters of patients with chronic nonspecific low back pain before and after treatment*

	Pretreatment	Post-treatment	*P*
Acetaminophen group (n = 23)			
CRP, mg/liter	1.6 ± 2.3	1.3 ± 1.1	0.55
ESR, mm/hour	6.2 ± 4.9	5.4 ± 4.3	0.14
TBP	6.3 ± 1.6	5.5 ± 2.3	0.04
ODI	21.1 ± 8.3	19.9 ± 8.7	0.22
BASDAI	4.8 ± 2	4.5 ± 2.1	0.15
BASFI	4.2 ± 4.6	3.1 ± 2.7	0.21
NBP	5 ± 2.2	5.1 ± 2.6	0.83
PGA	5.1 ± 1.9	4.6 ± 2.2	0.19
BASMI	1.6 ± 1.1	1.5 ± 1.6	0.85
SF-36 PCS	37.8 ± 11	40.6 ± 11	0.04
SF-36 MCS	48.5 ± 10	48.4 ± 10	0.92
Celecoxib group (n = 24)			
CRP level, mg/liter	2.2 ± 2.2	2.2 ± 2.4	1
ESR, mm/hour	5 ± 4.1	5.3 ± 4	0.72
TBP	6.6 ± 1.6	4.2 ± 2.6	< 0.001
ODI	20.4 ± 8.3	13.6 ± 8.8	< 0.001
BASDAI	4.7 ± 2	3.2 ± 2.2	< 0.001
BASFI	4.3 ± 4.4	2.4 ± 2.2	0.04
NBP	4.8 ± 2.3	3.2 ± 2.7	0.005
PGA	4.8 ± 2.8	3.2 ± 2.5	0.01
BASMI	1.25 ± 1.26	1.1 ± 0.9	0.33
SF-36 PCS	39.4 ± 9.4	43.8 ± 9.3	0.005
SF-36 MCS	44 ± 11.4	47.1 ± 12	0.25

* Values are the mean ± SD, unless indicated otherwise. See Table 1 for definitions.

Table 3. Comparison of acetaminophen versus celecoxib groups regarding their delta changes (post- and pretreatment difference)*

	Acetaminophen (n = 23)	Celecoxib (n = 24)	*P*
ΔCRP	0 (−10, 5)	0 (−7, 8)	0.93
ΔESR	−1 (−5, 4)	0 (−9, 10)	0.31
ΔTBP	−0.5 (−5, 2)	−2 (−8, 1)	0.04
ΔODI	0 (−8, 8)	−5 (−31, 4)	0.008
ΔBASDAI	−0.4 (−2.3, 1.9)	−1.1 (−5.4, 1.6)	0.03
ΔBASFI	−0.2 (−19, 3)	−0.4 (−20, 0.7)	0.26
ΔNBP	0 (−8, 8)	−1 (−7, 4)	0.01
ΔPGA	0 (−5, 3)	−2 (−6, 7)	0.04
ΔBASMI	0 (−2, 2)	0 (−2, 1)	0.8
ΔSF-36 PCS	3.5 (−10.9, 15.6)	3.9 (−11.5, 23.5)	0.81
ΔSF-36 MCS	0.5 (−12.8, 10.9)	0.5 (−17.6, 27.1)	0.42
ΔSpine score	0 (−3.5, 3.5)	0 (−5.5, 2)	0.27
ΔSIJ score	0 (−1, 1)	0 (−2.5, 3)	0.36

* Values are the median (minimum, maximum). See Table 1 for definitions.

Table 4. Percentage of patients with 50% reduction in various back pain scales and Guyatt's Responsiveness Index (GRI) for each back pain variable*

	Acetaminophen (n = 23)	Celecoxib (n = 24)	*P*	GRI
TBP	9.1	33.3	0.07	1.28
ODI	4.5	34.8	0.02	1.62
NBP	9.1	41.7	0.02	0.58
BASDAI	9.1	30.4	0.13	1.27

* Values are percentage, unless indicated otherwise. See Table 1 for definitions.

Acetaminophen arm. On the final assessment (day 28), patients treated with acetaminophen showed that TBP values were significantly decreased after the 4 weeks of treatment (6.3 ± 1.6 versus 5.5 ± 2.3; $P = 0.04$). There was also a significant improvement in SF-36 physical component summary after the acetaminophen therapy (37.8 ± 11 versus 40.6 ± 11; $P = 0.04$). On the other hand, acetaminophen use did not have a significant effect on ODI, NBP, patient global assessment, and SF-36 mental component summary ($P > 0.05$) (Table 2).

Celecoxib arm. Four weeks treatment of celecoxib therapy resulted in significant reductions in TBP, ODI, NBP, patient global assessment, BASDAI, and BASFI scores ($P < 0.05$) (Table 2). There was also a significant improvement in SF-36 physical component summary after the treatment ($P < 0.05$). However, BASMI, acute-phase proteins, and SF-36 mental component summary did not show any change with the use of celecoxib ($P > 0.05$). Table 2 summarizes the data regarding the effect of treatment on outcome variables in patients treated with acetaminophen and celecoxib.

Comparison of outcome parameters between acetaminophen and celecoxib groups. When we compared the magnitude of change (Δ = pre- and post-treatment difference) of different variables between the treatment groups, celecoxib use showed a greater decrease on TBP, ODI, BASDAI, NBP, and patient global assessment compared to acetaminophen-treated patients ($P < 0.05$) (Table 3). In addition, the number of patients with a significant change in back pain scales (≥50% reduction compared to baseline) was higher among celecoxib users than among subjects treated with acetaminophen (ODI 34.8% versus 4.5% [$P = 0.02$], NBP 41.7% versus 9.1% [$P = 0.02$], TBP 33.3% versus 9.1% [$P = 0.07$], and BASDAI 30.4% versus 9.1% [$P = 0.13$]). The responsiveness to celecoxib, calculated by GRI, was 1.62, 1.28, 1.27, and 0.58 for the ODI, TBP, BASDAI, and NBP, respectively. Table 4 shows the percentage of patients with 50% reduction in various back pain scales and responsiveness to treatment values estimated by GRI.

MRI study results. The reliability measures between the observers regarding MRI assessments were as follows: pre-spine 0.74, post-spine 0.7, pre-SIJ (SPARCC) 0.75, post-SIJ (SPARCC) 0.79, pre-SIJ (ASAS) 0.65, and post-SIJ (ASAS) 0.57. There were no changes in SPARCC spine and SIJ scores after the treatment when compared to baseline values ($P > 0.05$) (Table 5). According to the baseline evaluation, the frequency of patients with MRI SIJ and spine score ≥2 was 26.1% and 43.5% in the acetaminophen arm, and 16.7% and 65.2% in the celecoxib arm, respectively (Table 5). The number of patients with MRI SIJ and spine score ≥2 did not change after the treatment when compared with baseline values ($P > 0.05$) (Table 5). Baseline and followup evaluation of SIJs showed that a total of 20% and 22% of the patients fulfilled the ASAS/OMERACT sacroiliitis criteria, respectively. Both treatment groups showed similar response rates regarding sacroiliitis scores (Table 5). There were no correlations

Table 5. MRI spine and SIJ scores of patients with chronic NSLBP receiving acetaminophen and celecoxib*

	Pretreatment	Post-treatment	*P*1	*P*2	*P*3
SPARCC SIJ score, mean ± SD					
Acetaminophen	1.3 ± 1.9	1.4 ± 2	0.26	0.25	0.26
Celecoxib	0.75 ± 1.5	0.83 ± 1.4	0.13	0.25	0.26
SPARCC spine score, mean ± SD					
Acetaminophen	3.13 ± 4.4	3.03 ± 4.4	0.78	0.214	0.39
Celecoxib	5.2 ± 6.6	4.3 ± 5.8	0.07	0.214	0.39
SPARCC SIJ score ≥2					
Acetaminophen	26.1	26.1	1	0.49	1
Celecoxib	16.7	25	0.5	0.49	1
Sacroiliitis according to ASAS/OMERACT criteria					
Acetaminophen	21.7	21.7	1	0.72	1
Celecoxib	16.7	20.8	1	0.72	1
SPARCC spine score ≥2					
Acetaminophen	43.5	39.1	1	0.24	0.14
Celecoxib	65.2	65.2	1	0.24	0.14

* Values are percentage, unless indicated otherwise. *P*1 = comparison of pre- and post-treatment groups; *P*2 = comparison of acetaminophen and celecoxib patients prior to treatment; *P*3 = comparison of acetaminophen and celecoxib patients after treatment. MRI = magnetic resonance imaging; OMERACT = Outcome Measures in Rheumatology. See Table 1 for additional definitions.

noted between ΔSPARCC spine and SIJ changes, with Δ changes in ODI, NBP, TBP, and BASDAI ($P > 0.05$).

DISCUSSION

In this study of chronic NSLBP, we showed that celecoxib 200 mg twice daily was associated with greater improvement on back pain scales compared to acetaminophen 500 mg twice daily. Patients treated with celecoxib for 4 weeks showed a greater improvement in pain scores as well as disability, as shown in BASDAI, TBP, ODI, and NBP, compared with the patients treated with acetaminophen. In addition to the numerical change, the frequency of patients who had achieved the therapeutic target with at least 50% improvement in NBP and ODI was also greater in the group of patients treated with celecoxib. Celecoxib treatment demonstrated that 40% of patients reached therapeutic targets on defined outcome measures, whereas acetaminophen achieved the targets in less than 10%. Both drugs showed significant effect on TBP scale, but direct comparison between celecoxib and acetaminophen effect showed more significant relief of pain in the celecoxib-treated group. Our results were also consistent when we analyzed the effect size for each back pain scale. According to GRI statistics, ODI, TBP, and BASDAI showed large effect sizes and NBP moderate effect size with celecoxib treatment.

Our results are in keeping with prior studies that showed superiority of NSAIDS over the placebo on chronic LBP (12,23–28). In our study, we compared celecoxib 200 mg twice daily with acetaminophen 500 mg twice daily. In the literature to date, data regarding the comparison of NSAIDs versus paracetamol in chronic NSLBP patients are limited. There is only one study addressing this issue (27). In that study, Hickey (27) compared diflunisal (500 mg twice daily) with paracetamol (1,000 mg, 4 times daily), which revealed a superior effect in favor of diflunisal after 4 weeks of treatment. We are aware that the selected dose of acetaminophen in our study may not be sufficient to provide pain relief. A systematic review assessed the efficacy of paracetamol for patients with NSLBP. Only 7 trials (5 acute LBP, 1 chronic LBP, and 1 with both acute and chronic LBP) met the requirements for that study. Based on the review, there was no standardized, established dose for paracetamol (ranging from 1,000 mg/day to 6,000 mg/day), length of treatment was quite variable (ranging from 2 days to 4 weeks), and comparator treatment was also varied in the studies (NSAIDs, opioids, tricyclic antidepressants, and nonpharmacologic treatment approaches). According to the results, acetaminophen failed to show effectiveness in the treatment of NSLBP (29).

None of our cases discontinued the therapy over the 4-week trial, and no adverse reactions were recorded. Neither treatment showed any impact on inflammatory markers, but baseline CRP level and ESR were within normal limits. Morning stiffness as an indicator of active inflammation did not change with either celecoxib or acetaminophen therapy but was minimal at baseline. Acetaminophen showed improvement in terms of TBP but failed to show any effect on disability index, NBP, or patient global assessment. Compared to acetaminophen, celecoxib showed superiority in terms of improving disability index, NBP, and patient global assessment. This study also provided an opportunity to evaluate MRI in a cohort of chronic NSLBP patients. Spinal and SIJ scoring was done according to the SPARCC protocol (19,21). The proposed cutoff criteria of ≥2 were used to define positive spine and SIJ scores (22). We also evaluated MRI of the SIJs according to the ASAS/OMERACT definition (20). Based on our results, before the treatment, 55.1% of patients (65.2% taking celecoxib and 43.5% taking acetaminophen) had a SPARCC spine score ≥2. Four weeks of treatment did not change the frequency of spine lesions on MRI (total 55.1%, celecoxib 65.2%, and acetaminophen 43.5%). Similarly, the number of patients fulfilling the SPARCC SIJ score ≥2 at baseline did not change (total 21.3%, celecoxib 16.7%, and acetaminophen 26.1%) after the treatment (total 25.5%, celecoxib 25%, and acetaminophen 26.1%). In our study population, 20% and 22% of chronic NSLBP patients fulfilled the ASAS/OMERACT-defined criteria of SIJ inflammation at baseline and followup, respectively. If the ASAS definition of axial SpA is used (30), 1 patient (in the acetaminophen group) had an elevated CRP level, which might be considered to fulfill the classification criteria for the imaging arm of axial SpA at both pre- and post-treatment time points. But the expert opinion of the clinician was that the back pain was more likely NSLBP than axial SpA.

In addition, we found no association between the spinal and SIJ inflammatory lesions and clinical response. The high frequency of spinal and SIJ positivity in healthy controls and NSLBP populations was also reported in previous MRI studies. Weber et al (9) reported that nearly 50% of the NSLBP pain patients and 40% of the healthy controls had ≥2 corner inflammatory lesions in the spine. In a subsequent study, 30% of healthy controls and 23.1% of patients with nonspecific back pain fulfilled the ASAS criteria for the positive SIJ inflammation (31). A recent study, examining 1,037 LBP patients, reported 21.7% of the group had detectable bone marrow edema on SIJs (32). Despite the reported high frequencies, the clinical significance of spinal inflammatory lesions observed in chronic NSLBP patients remains undefined. Some studies investigated the diagnostic performance of different cutoff values for corner inflammatory lesions and suggested that a value of ≥6 had moderate to substantial diagnostic utility for differentiating nonradiographic axial SpA from NSLBP (9). In the current study, the inclusion criteria were designed to target patients with chronic NSLBP of a certain severity and duration. LBP patients were questioned carefully for the presence of features of inflammatory back pain and for other clinical features of SpA. HLA–B27 was negative in all patients studied, with one exception, pelvic radiographs were negative for sacroiliitis, and family histories were negative for SpA. In addition, there were no other underlying specific conditions present to explain the LBP. In the absence of inflammatory symptoms, and the presence of normal acute-phase proteins, the detected inflammatory changes on MRI suggest a local pathology rather than a systemic etiology.

Thus the diagnosis of chronic NSLBP was consistent with current diagnostic frameworks. We acknowledge certain limitations of the current study. First, our study excluded patients with inflammatory back pain. As a result, we do not know whether the presence or absence of inflammatory

symptoms may suggest an increased efficacy of NSAIDs with respect to MRI changes or clinical measurements. Second, as mentioned previously, the acetaminophen dosage (500 mg twice daily) was not the maximum dosage allowed, when compared to celecoxib, which was used in full dose. Future studies could consider higher doses of acetaminophen to allow for a more quantitative comparison. Third, we did not assess the presence of spinal degenerative changes, and we cannot conclude whether these changes have an effect on the efficacy of NSAIDs. Fourth, as there is no established imaging scoring system for MRI in NSLBP patients, our study used the SPARCC scoring system. This scoring system has only been applied in axial SpA and has not been validated in NSLBP. Nonetheless, this method was used in the absence of a more suitable scoring method.

In conclusion, there was superior efficacy of celecoxib compared with acetaminophen in chronic NSLBP. Inflammatory lesions of SIJs and spine can be commonly seen in NSLBP, but these lesions were not improved with either celecoxib or acetaminophen treatments and were not associated with clinical response to either agent.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Inman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Bedaiwi, Wallis, O'Shea, Haroon, Inman.

Acquisition of data. Bedaiwi, Sari, Inman.

Analysis and interpretation of data. Bedaiwi, Sari, Salonen, Haroon, Omar, Inman.

ROLE OF THE STUDY SPONSOR

Pfizer had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Pfizer.

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