Research Article

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Efficacy and tolerability of celecoxib in osteoarthritis patients who previously failed naproxen and ibuprofen: results from two trials

Michael J Asmus[1], Margaret Noyes Essex[1], Pritha Bhadra Brown[1] & Sharon R Mallen*[,1]
[1]Pfizer Inc., New York, NY 10017, USA
*Author for correspondence:
Tel.: +1 212 733 3211
Fax: +1 212 338 1602
sharon.mallen@pfizer.com

Aims: To evaluate the efficacy and safety of celecoxib in patients with osteoarthritis who previously failed naproxen and ibuprofen treatment. **Materials & methods:** Two identical, 6-week, randomized, double-blind, placebo-controlled trials of celecoxib 200 mg daily were undertaken in patients with knee osteoarthritis. The primary efficacy variable was the 6-week change in Patient's Assessment of Arthritis Pain visual analog scale. **Results:** In study 1 (n = 370), the visual analog scale least squares mean decrease from baseline was 27.3 (celecoxib) versus 14.9 mm (placebo; $p < 0.001$); it was 28.0 versus 24.6 mm, respectively, in study 2 (n = 380). **Conclusion:** Celecoxib was well tolerated, yet the efficacy results differed, highlighting the complexities of treating patients with osteoarthritis who have failed previous NSAID treatment.

Keywords: knee • nonresponder • NSAIDs • osteoarthritis • pain • treatment failure

Background

Osteoarthritis (OA) is the most common form of arthritis, affecting a third of those aged ≥65 years [1]. The goal of pharmacologic treatment is to decrease the pain and inflammation associated with OA. By reducing these symptoms, a patient's physical function can be improved.

The Osteoarthritis Research Society International expert consensus guidelines recommend either a COX-2-selective agent or a nonselective NSAID (depending on the presence of cardiovascular or gastrointestinal [GI] risk factors) for the management of OA of the hip and knee [2]. Celecoxib, a COX-2-selective NSAID, has demonstrated comparable efficacy in OA of the knee versus naproxen [3,4] and versus ibuprofen [5].

In some patients, intolerability to NSAIDs can limit the options for treating their OA symptoms. All NSAIDs carry a risk of serious GI side effects such as bleeding; however, abdominal pain, nausea and dyspepsia are the more common GI tolerability-related side effects, and these can limit the duration of treatment. Some managed-care criteria reserve the use of celecoxib as a second- or third-line NSAID when other NSAIDs have failed or are not tolerated.

In this report of two identical studies, we mimic real-world clinical practice by evaluating the efficacy of celecoxib in patients with OA of the knee who previously were nonresponsive to or did not tolerate treatments with prescription-strength doses of both naproxen and ibuprofen. The objective is to compare patients' assessments of arthritis pain (visual analog scale [VAS]) after 6 weeks of celecoxib 200 mg once daily (q.d.) or placebo.

Materials & methods

Study design

Patients were randomized at baseline (1:1) to receive celecoxib 200 mg q.d. or placebo for 6 weeks in two identically designed, concurrent, double-blind, parallel-group, multicenter studies (study 1 and 2). There were four study visits: screening (visit 1, 1–14 days prior to the first dose of study medication), baseline (visit 2, day 0, within 24 h of the first dose of study medication),

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week 2 (visit 3, day 14 ± 2 after the first dose of study medication) and week 6 (visit 4, day 42 ± 4 after the first dose of study medication). For patients who terminated early, the week 6 assessments were performed at termination.

Patients

Patients aged ≥40 years with diagnosed, active, symptomatic OA of the knee in a flare state, as determined by American College of Rheumatology criteria [6], were enrolled according to the following inclusion criteria: had failed prior treatment with both prescription strength naproxen (at least 750 mg/day for 2 weeks) and ibuprofen (at least 1200 mg/day for 2 weeks) within the past 5 years due to either lack of efficacy and/or tolerability; females of childbearing potential had a negative urine pregnancy test and had to be using an adequate method of contraception; if taking chronic NSAID therapy, patients were to complete a wash-out period for a minimum of 2 days; patients were to have a functional capacity class of I–III; a willingness to participate for 6 weeks and ability to provide informed consent. Exclusion criteria were: inflammatory arthritis or gout/pseudo-gout with an acute flare in the past 2 years; active symptomatic acute joint trauma in the index joint within past 3 months; previous or anticipated need for surgery on the index joint (knee arthroscopy for reasons other than arthritis was permitted as long as it was performed at least 90 days prior to screening); treatment with oral (4 weeks), intramuscular (2 months), intra-articular (3 months) or soft-tissue (2 months) injection of corticosteroids or intra-articular injection of hyaluronic acid in the index joint within 9 months of first dose of study medication; use of acetaminophen within 24 h of the baseline visit; treatment with anticoagulants, lithium, glucosamine and/or chondroitin sulfate; malignancy; treatment for esophageal, gastric, pyloric channel or duodenal ulceration; GI or cardiovascular disease; having >1.5 times the upper limit of normal for aspartate aminotransferase, alanine aminotransferase or other clinically significant laboratory abnormalities; known sensitivity to COX-2 inhibitors or related compounds; use of study drug in the past 30 days; participation in physical therapy for the index joint and use of a mobility-assisting device <6 weeks prior to the study.

Study end points

The primary efficacy end point was change from baseline to week 6 in the Patient's Assessment of Arthritis Pain (VAS, measured on a 0 [no pain] to 100 [very severe pain] mm scale).

Secondary end points included the change in Western Ontario and McMaster Universities (WOMAC) OA Index from baseline to week 6, and the change in Patient's and Physician's Global Assessment of Pain from baseline to week 6.

Statistical analysis

Identical statistical plans were followed for study 1 and 2, but distinct analyses were carried out on each data set. Analyses were performed on the modified intent-to-treat population defined as patients who had been randomized, received at least one dose of study medication, and had at least one post baseline pain assessment. The primary outcome was analyzed using a general linear model with effects for treatment, center and baseline VAS score in the model. Missing values were imputed using last observation carried forward. The differences in the least squares mean (LSM), standard error of the differences, two-sided 95% CI for the difference and p-values are presented.

WOMAC scores for the two treatment groups (celecoxib vs placebo) were compared and p-values, differences in the LSM, standard errors of the differences and 95% CIs for the differences are presented.

Classification of Patient's Global Assessment and Physician's Global Assessment were analyzed using the Cochran–Mantel–Haenszel test (row-mean-score-test), stratified by center.

Results

Patient disposition

Study 1

A total of 380 patients were randomized from 29 centers in the USA. Two patients in the celecoxib group and three in the placebo group were not treated. Discontinuations relating to study drug were higher for placebo than for celecoxib (Table 1), with more patients who received placebo discontinuing due to lack of efficacy (11.1%) compared with those who were treated with celecoxib (3.2%).

Study 2

A total of 388 patients were randomized from 30 centers in the USA. One patient in the celecoxib group and two in the placebo group were not treated. Discontinuations relating to study drug were higher for placebo than for the celecoxib group (Table 1), with more patients who received placebo discontinuing due to lack of efficacy (15.0%) compared with those who were treated with celecoxib (4.1%).

Baseline demographics

Baseline age was similar and the majority of patients were female in both studies. More nonwhite patients were enrolled in study 2 compared with study 1 (Table 2).

Table 1. Disposition of patients.

Characteristic	Study 1		Study 2	
	Celecoxib 200 mg q.d.	Placebo	Celecoxib 200 mg q.d.	Placebo
Randomized, n	190	190	195	193
Treated, n	188	187	194	191
Completed, n (%)†	153 (81.4)	125 (66.8)	157 (80.9)	137 (71.7)
Discontinued, n (%)‡	37 (19.5)	65 (34.2)	38 (19.5)	56 (29.0)
– Related to study drug	8 (4.2)	26 (13.7)	11 (5.6)	35 (18.1)
– Adverse event	2 (1.1)	5 (2.6)	3 (1.5)	6 (3.1)
– Lack of efficacy	6 (3.2)	21 (11.1)	8 (4.1)	29 (15.0)
– Not related to study drug	29 (15.3)	39 (20.5)	27 (13.8)	21 (10.9)
– Adverse event	3 (1.6)	3 (1.6)	3 (1.5)	6 (3.1)
– Other reasons	19 (10.0)	19 (10.0)	21 (10.8)	10 (5.2)
– Patient defaulted	7 (3.7)	17 (8.9)	3 (1.5)	5 (2.6)

†Calculated based on the number of treated patients.
‡Calculated based on the number of randomized patients.
q.d.: Once daily.

Patient's Assessment of Arthritis Pain (VAS)

Study 1

At week 6, the improvement from baseline in the Patient's Assessment of Arthritis Pain (VAS) in the celecoxib group (n = 186) was significantly better, compared with placebo (n = 184; LSM change -27.3 vs -14.9 mm; p < 0.001) (Figure 1).

Study 2

At week 6, the improvement from baseline in the Patient's Assessment of Arthritis Pain (VAS) in the celecoxib group (n = 194) was no different from placebo (n = 186; LSM change -28.0 vs -24.6 mm; p = 0.183) (Figure 1).

WOMAC OA index

Study 1

Improvement from baseline to week 6 was significantly better for celecoxib than placebo for the total WOMAC score and all subscales (p < 0.001) (Table 3).

Study 2

Improvement from baseline to week 6 was significantly better for celecoxib and placebo for the total WOMAC score and for the stiffness and physical function subscales, but the difference in the pain subscale was not significant (Table 3).

Patient's & Physician's Global Assessment of Arthritis Pain

Study 1

A larger proportion of patients reported an improvement in the celecoxib than in the placebo group (37.0 and 26.3%, respectively; p = 0.006) based on the Patient's Global Assessment of Arthritis (Table 4). A larger proportion of patients in the celecoxib group than in the placebo group had an improvement as assessed by their physician (38.5 and 27.3%, respectively, p = 0.020) using the Physician's Global Assessment of Arthritis (Table 4).

Study 2

Based on the Patient's Global Assessment of Arthritis, a similar proportion of patients in both the celecoxib and the placebo group reported an improvement (45.1 and 43.2%, respectively; p = 0.746) (Table 4). The Physician's Global Assessment of Arthritis also showed that the proportion of patients who had an improvement was similar between groups (celecoxib 46.6 and placebo 41.1%; p = 0.229) (Table 4).

Safety assessments

Study 1

The proportion of patients reporting at least one adverse event (AE) was similar between the celecoxib and placebo groups (all causality: 25.0 and 25.1%, respectively; treatment-related: 6.4 and 5.3%, respectively). The proportions of patients who discontinued due to AEs in the celecoxib and placebo groups were as follows: all causality: 2.7 and 4.8%, respectively; treatment-related: 1.1 and 2.7%, respectively. Treatment-related AEs that led to discontinuation were: upper abdominal pain, abdominal distension, GI pain, gastritis, change of bowel habit, arthralgia, back pain and urticaria.

There were no deaths during this study and treatment-emergent serious AEs were reported for two

Table 2. Patient demographics.

Characteristic	Study 1		Study 2	
	Celecoxib 200 mg q.d. (n = 190)	Placebo (n = 190)	Celecoxib 200 mg q.d. (n = 195)	Placebo (n = 193)
Age, years, mean (SD)	60.6 (9.6)	60.0 (10.5)	58.8 (9.8)	58.4 (10.2)
Sex, n (%)				
– Male	72 (37.9)	78 (41.1)	56 (28.7)	69 (35.8)
– Female	118 (62.1)	112 (58.9)	139 (71.3)	124 (64.2)
Race/ethnic origin, n (%)				
– White	136 (71.6)	140 (73.7)	101 (51.8)	109 (56.5)
– Black	17 (8.9)	19 (10.0)	50 (25.6)	38 (19.7)
– Asian	12 (6.3)	9 (4.7)	20 (10.3)	20 (10.4)
– Other	25 (13.2)	22 (11.6)	24 (12.3)	26 (13.5)
Patient's Assessment of Arthritis Pain (VAS)†, mm, mean (SD)	66.5 (12.6)	66.8 (11.4)	68.3 (11.6)	67.4 (12.4)
WOMAC: total domain score‡, mean (SD)	54.1 (14.0)	52.2 (15.0)	80.9 (13.5)	78.7 (13.5)
Duration of OA, mean (range)	8.5 (0.1–42)	9.4 (0.2–64.2)	6.7 (0.0–47.1)	7.0 (0.0–51.3)

†Scale ranged from 0 to 100 mm, with lower score being better.
‡Total domain score is the sum of pain, stiffness and physical function domain scores.
OA: Osteoarthritis; q.d.: Once daily; SD: Standard deviation; VAS: Visual analog scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

patients. A 78-year-old man in the celecoxib group had a cerebrovascular accident, hypoesthesia and arteriosclerosis. A 68-year-old man in the placebo group had colon cancer. In both cases the investigators concluded that these AEs were not related to the study treatment.

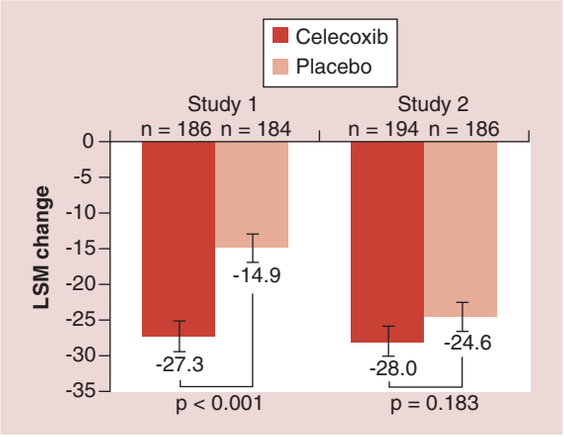

Figure 1. Least squares mean change from baseline to week 6 in the Patient's Assessment of Arthritis Pain (visual analog scale; modified intent-to-treat population). LSM and p-values are from a general linear model with treatment and pooled center as factors and the baseline value as covariate.
LSM: Least squares mean.

Study 2

The proportion of patients reporting at least one AE in the celecoxib group was lower than that in the placebo group, especially for treatment-related AEs (all causality: 22.2 and 26.2%, respectively; treatment-related: 6.2 and 11.5%, respectively). The proportion of patients who discontinued due to an AE in the celecoxib and placebo groups were as follows: all causality: 3.1 and 6.3%, respectively; treatment-related: 2.1 and 3.1%, respectively. Treatment-related AEs that led to study discontinuation were: abdominal pain, upper abdominal pain, abdominal distension, GI discomfort, diarrhea, flatulence, cough, dyspnea, asthenia, malaise, headache, erythema and somnolence.

There were no deaths during this study and treatment-emergent serious AEs were reported for two patients. A 55-year-old man in the celecoxib group had peripheral vascular disease, arterial occlusion, ischemia/ulcer on his left fifth toe, as well as superficial femoral artery occlusion requiring hospitalization. An 86-year-old man in the placebo group had a transient ischemic attack, ataxia and atherosclerosis requiring hospitalization. In both cases the investigators concluded that these AEs were not related to the study treatment.

Table 3. Least squares mean change from baseline to week 6 in Western Ontario and McMaster Universities Osteoarthritis Index total and subscales (modified intent-to-treat population).

Treatment effects (celecoxib–placebo)	Study 1: celecoxib, n = 186; placebo, n = 184			Study 2: celecoxib, n = 194; placebo, n = 186		
	LSM (SE) difference	95% CI	p-value	LSM (SE) difference	95% CI	p-value
Total	-10.7 (2.0)	-14.6 to -6.8	<0.001	-3.6 (1.7)	-7.0 to -0.24	0.036
Pain	-2.3 (0.42)	-3.2 to -1.5	<0.001	-0.8 (0.39)	-1.5 to 0.008	0.052
Stiffness	-0.9 (0.18)	-1.3 to -0.55	<0.001	-0.4 (0.17)	-0.71 to -0.041	0.028
Physical function	-7.5 (1.4)	-10.3 to -4.6	<0.001	-2.4 (1.2)	-4.9 to -0.006	0.049

LSM and p-value are from a general linear model with treatment and pooled center as factors and the baseline value as a covariate.
LSM: Least squares mean; SE: Standard error.

Post-hoc analysis to understand divergent results

While study 1 and 2 were identical in design, the primary efficacy results differed. Study 1 showed that celecoxib 200 mg q.d. was statistically significantly better than placebo based on patients' assessment of pain (VAS) from baseline to week 6. In study 2, there was no difference between celecoxib and placebo. The most apparent difference between these studies was in the baseline demographic characteristics of the study population, with study 2 having a higher number of nonwhite patients than study 1 (Table 2). Therefore, a post-hoc analysis was performed for study 2, evaluating the efficacy of celecoxib in white patients separately from nonwhite patients.

Of the 388 randomized patients in study 2, there were 210 white patients (101 in the celecoxib group and 109 in the placebo group) and 178 nonwhite patients (94 in the celecoxib group and 84 in the placebo group). In both treatment groups, more white patients withdrew from the study than nonwhite patients.

For the primary efficacy variable, mean change from baseline in the Patient's Assessment of Arthritis Pain (VAS) at week 6, there was no significant difference between celecoxib and placebo for either the white patients (difference in LSM between celecoxib [n = 100] and placebo [n = 103] -4.5; SE: 3.83; p = 0.243) or the nonwhite patients (difference in LSM between celecoxib [n = 94] and placebo [n = 83] 0; SE: 3.31; p = 0.992) in the modified intent-to-treat population. For the secondary end point of WOMAC, there was a statistically significant difference between the celecoxib and placebo treatment groups in the total score and all three domain scores (pain, stiffness, physical function), for white patients ($p < 0.05$). There was no statistically significant difference between the treatment groups for nonwhite patients.

Discussion

This evaluation of two identically designed, concurrent, controlled trials of celecoxib 200 mg q.d. versus placebo in patients with OA who previously did not respond to, or did not tolerate, naproxen and ibuprofen, gave mixed results.

In study 1, celecoxib was more effective than placebo for the primary end point of Patient's Assessment of Arthritis Pain (VAS), as well as for the secondary end point of WOMAC. In study 2, celecoxib was not statistically different from placebo for the primary end point of Patient's Assessment of Arthritis Pain (VAS). Although celecoxib was more effective than placebo for total WOMAC and the stiffness and physical function WOMAC subscales, there was no significant difference in the pain subscale for study 2.

It was considered possible that variations in ethnic demographics between the participants of the two studies might explain differences in response. In study 1, 71.6% of patients who received celecoxib were white, while white patients made up 51.8% of the celecoxib group in study 2. Approximately a quarter of patients in study 2 who received celecoxib were black, compared with approximately 9% of the celecoxib-treated patients in study 1. To specifically address the influence of ethnicity, a post-hoc analysis was undertaken to evaluate the efficacy of celecoxib in white patients separately from nonwhite patients. When patients were stratified in this way, there was no significant difference between celecoxib and placebo for the Patient's Assessment of Arthritis Pain (VAS) in either whites or nonwhites, consistent with the primary results for all patients together. For WOMAC, white patients who received celecoxib had significantly greater improvements in total and individual domain scores compared with white patients who received placebo. This was similar to the WOMAC results for all patients together with the exception of the pain subscale. For nonwhite patients, however, there were no

Table 4. Patient's and Physician's Global Assessment of Arthritis at week 6 (or early termination) and change from baseline to week 6 (modified intent-to-treat population).

	Study 1			Study 2		
	Celecoxib 200 mg q.d. (n = 186)	Placebo (n = 184)	p-value†	Celecoxib 200 mg q.d. (n = 194)	Placebo (n = 186)	p-value†
Patient's Global Assessment of Arthritis, n (%)						
Very good	17 (9.2)	11 (6.1)	0.003	12 (6.2)	7 (3.8)	0.027
Good	65 (35.3)	47 (26.3)		78 (40.4)	73 (39.9)	
Fair	72 (39.1)	72 (40.2)		78 (40.4)	71 (38.8)	
Poor	27 (14.7)	35 (19.6)		22 (11.4)	30 (16.4)	
Very poor	3 (1.6)	14 (7.8)		3 (1.6)	2 (1.1)	
Change from baseline						
Improved	68 (37.0)	47 (26.3)	0.006	87 (45.1)	79 (43.2)	0.746
No change	113 (61.4)	122 (68.2)		105 (54.4)	104 (56.8)	
Worsened	3 (1.6)	10 (5.6)		1 (0.5)	0 (0)	
Physician's Global Assessment of Arthritis, n (%)						
Very good	19 (10.4)	8 (4.5)	0.049	14 (7.3)	10 (5.6)	0.235
Good	70 (38.5)	47 (26.7)		88 (45.6)	71 (39.4)	
Fair	67 (36.8)	64 (36.4)		68 (35.2)	65 (36.1)	
Poor	22 (12.1)	49 (27.8)		22 (11.4)	33 (18.3)	
Very poor	4 (2.2)	8 (4.5)		1 (0.5)	1 (0.6)	
Change from baseline, n (%)						
Improved	70 (38.5)	48 (27.3)	0.020	90 (46.6)	74 (41.1)	0.229
No change	109 (59.9)	121 (68.8)		102 (52.8)	105 (58.3)	
Worsened	3 (1.6)	7 (4.0)		1 (0.5)	1 (0.6)	

†Cochran–Mantel–Haenszel (row-mean-score-difference) test, stratified by center.
q.d.: Once daily.

statistically significant differences between celecoxib and placebo in WOMAC. Given the mixed results of the post-hoc analysis of the Patient's Assessment of Arthritis Pain (VAS) and WOMAC scores in white and nonwhite patients, it is not clear if ethnicity had an influence on the efficacy of celecoxib.

Inconsistencies in the experience of pain between different ethnic groups are known to exist [7–9]. In a study of African–American patients with OA of the knee, celecoxib was as effective as naproxen in relieving pain, but neither active treatment group was significantly different than placebo [10]. This lack of significance between active treatment groups and placebo was thought to be due to a high placebo response in this African–American population. Study 2 of this current report also showed a high placebo response compared with study 1. Perhaps the greater proportion of black patients in study 2 compared with study 1 may have been a factor contributing to the higher placebo response observed in study 2. Regardless of ethnicity, placebo response is a common feature of studies that investigate treatments for pain, which can complicate the conduct of trials and confound results. In a meta-analysis of 198 trials of nonpharmacologic, pharmacologic and invasive treatments for OA, a large effect on pain relief was observed among patients who received placebo (effect size: 0.51, 95% CI: 0.46–0.55 for the placebo group; effect size: 0.03, 95% CI: -0.13–0.18 for untreated controls). Placebo also led to improvements in other measures such as function, stiffness and even physician's global assessment [11]. The findings of this meta-analysis support our observations from studies 1 and 2, and confirm the appreciable effect that placebo can have on relieving some symptoms of OA.

A limitation of these current studies was their relatively short duration of 6 weeks; most patients with OA need to take medication on a chronic basis. Another limitation was that the study did not capture the number of patients who entered due to lack of efficacy versus intolerance to naproxen and ibuprofen, nor was the reason for intolerance collected (e.g., GI side

effects, hypertension). These data may have been useful to further explain the different outcomes between studies 1 and 2.

Patients vary in their responses to different NSAIDs and there can be variability in how different patients respond to the same NSAID. For these reasons it is important to have several treatment options available in the clinicians' armamentarium. The latest American College of Rheumatology guidelines for the treatment of OA of the hand, hip and knee do not state an optimal pharmacologic sequence that should be followed for patients who have an inadequate response to initial treatments, due to the paucity of clinical trial data that would support such recommendations [12]. The studies described in this report are pertinent to real-world practice, where patients often receive nonselective NSAIDs, such as naproxen and ibuprofen, before receiving celecoxib. These studies suggest that some patients who have previously failed therapy with naproxen and ibuprofen may respond to celecoxib.

Conclusion

The results demonstrate that celecoxib can be an effective alternative for some patients with OA who have previously failed to respond or who have previously not tolerated both ibuprofen and naproxen. The discordant efficacy results between the two studies highlight the challenges that are inherent to treating OA.

Future perspective

In the next 5–10 years, we expect clinical practice guidelines for OA to be refined, to provide specific recommendations on the pharmacologic management of patients who do not respond to first-line NSAIDs.

Financial & competing interests disclosure

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

Background

- In real-world practice, clinicians often prescribe a nonselective NSAID for patients with osteoarthritis (OA) before the COX-2-selective NSAID, celecoxib, is offered.
- In this report of two identically designed trials, the efficacy of celecoxib in patients who previously did not respond to or tolerate naproxen and ibuprofen was evaluated.

Materials & methods

- Patients aged ≥40 years with OA of the knee were randomized to receive celecoxib 200 mg once daily or placebo for 6 weeks in concurrent, double-blind studies.
- The primary efficacy outcome was the change from baseline to week 6 in the Patient's Assessment of Arthritis Pain using a visual analog scale (VAS), measured from 0–100 mm.
- A post-hoc analysis of study 2 stratified patients by ethnicity (white and nonwhite).

Results

- In study 1, celecoxib demonstrated a significant improvement from baseline to week 6 in the Patient's Assessment of Arthritis Pain (VAS; -27.3 vs -14.9 mm; $p < 0.001$).
- In study 2, the improvement from baseline to week 6 in the Patient's Assessment of Arthritis Pain (VAS) was no different between celecoxib and placebo (-28.0 vs -24.6 mm; $p = 0.183$).
- Study 2 had greater percentage of nonwhite patients than study 1. When white and nonwhite patients were analyzed separately in study 2, there was no significant difference between celecoxib and placebo for either white or nonwhite patients in the Patient's Assessment of Arthritis Pain (VAS).

Discussion

- Results varied between the two studies, possibly due to a high placebo response and greater percentage of nonwhite patients in study 2 compared with study 1.
- Lack of data regarding number of patients enrolled due to nonresponsiveness versus intolerance to naproxen and ibuprofen was a limitation that may have provided insight to help explain the varied results between the two studies.

Conclusion

- These studies highlight the challenges faced by clinicians when treating OA patients.

References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest

1 Centers for Disease Control and Prevention. Osteoarthritis. Division of Adult and Community Health, National Center for Chronic Disease Prevention and Health Promotion. www.cdc.gov/arthritis/basics/osteoarthritis.htm

2 Zhang W, Moskowitz RW, Nuki G *et al.* OARSI recommendations for the management of hip and knee osteoarthritis. Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage* 16, 137–162 (2008).

3 Zhao SZ, McMillen JI, Markenson JA *et al.* Evaluation of the functional status aspects of health-related quality of life of patients with osteoarthritis treated with celecoxib. *Pharmacotherapy* 19, 1269–1278 (1999).

4 Bensen WG, Fiechtner JJ, McMillen JI *et al.* Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: a randomized controlled trial. *Mayo Clin. Proc.* 74, 1095–1105 (1999).

•• **A 12-week randomized, double-blind, placebo-controlled trial that demonstrated superior efficacy of celecoxib versus placebo and comparable efficacy of celecoxib versus naproxen for reducing patients' osteoarthritis pain.**

5 Martin-Mola E, Munoz-Gomez J, Sanchez-Burson J *et al.* Celecoxib is as effective as ibuprofen in treating pain associated with osteoarthritis of the knee. Presented at: *The European League Against Rheumatism*. Vienna, Austria, 8–11 June 2005.

6 Altman R, Asch E, Bloch D *et al.* Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and therapeutic criteria committee of the American Rheumatism Association. *Arthritis Rheum.* 29, 1039–1049 (1986).

7 Golightly YM, Dominick KL. Racial variations in self-reported osteoarthritis symptom severity among veterans. *Aging Clin. Exp. Res.* 17, 264–269 (2005).

8 Edwards CL, Fillingim RB, Keefe F. Race, ethnicity and pain. *Pain* 94, 133–137 (2001).

9 Creamer P, Lethbridge-Cejku M, Hochberg MC. Determinants of pain severity in knee osteoarthritis: effect of demographic and psychosocial variables using 3 pain measures. *J. Rheumatol.* 26, 1785–1792 (1999).

10 Essex MN, O'Connell M, Bhadra BP. Response to nonsteroidal anti-inflammatory drugs in African Americans with osteoarthritis of the knee. *J. Int. Med. Res.* 40, 2251–2266 (2012).

• **A 6-week randomized, double-blind, placebo-controlled trial that demonstrated comparable efficacy of celecoxib versus naproxen in African–American patients. Nonsignificant differences between active treatments and placebo for Patient's Assessment of Arthritis Pain may be explained by the high placebo response rate.**

11 Zhang W, Robertson J, Jones AC, Dieppe PA, Doherty M. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. *Ann. Rheum. Dis.* 67, 1716–1723 (2008).

12 Hochberg MC, Altman RD, April KT *et al.* American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res. (Hoboken)* 64, 465–474 (2012).

•• **Clinical practice guidelines that include recommendations for the treatment of osteoarthritis with oral and topical NSAIDs. Provides an update to the American College of Rheumatology recommendations that were developed in 2000.**