Efficacy and tolerability of lumiracoxib versus placebo in patients with osteoarthritis of the hand

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Abstract

Objective

This multicentre, randomized, double-blind, placebo-controlled parallel-group study was undertaken to investigate the efficacy, safety and tolerability of lumiracoxib (Prexige®), a cyclooxygenase-2 selective inhibitor, in patients with primary osteoarthritis (OA) of the hand.

Methods

The study randomized 594 patients aged ≥ 18 years with symptomatic OA of the hand. Patients underwent a 3 to 7-day washout for previous nonsteroidal anti-inflammatory drugs and those with pain intensity ≥ 40 mm on a 100 mm Visual Analogue Scale (VAS) in the target hand during the 24 hours prior to baseline and an increase in pain intensity of either ≥ 20% or ≥ 10 mm VAS since screening (whichever was greater) were randomized to lumiracoxib 200 mg once daily (od) (n=205), lumiracoxib 400 mg od (n=193) or placebo (n=196). The primary efficacy variable was overall OA pain intensity (VAS mm) in the target hand after 4 weeks of treatment. Safety and tolerability assessments were performed.

Results

After 4 weeks of treatment, overall OA pain intensity in the target hand was significantly lower for patients treated with lumiracoxib compared with patients treated with placebo (both doses p<0.001). There was no significant difference between lumiracoxib doses in terms of the reduction in overall OA pain intensity. Lumiracoxib was well tolerated. The incidence of adverse events was similar for active treatment groups and placebo.

Conclusions

Lumiracoxib 200 and 400 mg od were effective and well tolerated treatments for OA of the hand. Lumiracoxib significantly improved overall OA pain intensity in the target hand versus placebo, with a tolerability profile similar to placebo.

Key words

Osteoarthritis, hand, non-steroidal anti-inflammatory agents, cyclooxygenase inhibitors, pain, analgesics.

Introduction

Osteoarthritis (OA) is a highly prevalent, chronic and progressive musculoskeletal disease characterized by joint pain and stiffness (1). OA affecting the hand is a particularly disabling form of the disease as the level of joint pain and stiffness directly affects manual dexterity (2). The resulting limitations in performing activities of daily living may have a considerable impact on quality of life (QoL) and general patient well-being (3). Furthermore, the clinical manifestation of hand OA (pain, stiffness and physical function/disability) is distinct from other types of OA such as knee or hip (3-5). As such, it is important to establish the clinical benefits of a therapeutic regimen in hand OA, in addition to separate assessment of efficacy in other types of OA.

Cyclooxygenase-2 (COX-2) selective inhibitors were developed as treatments for both acute and chronic pain, with the objective of providing efficacy similar to traditional nonsteroidal anti-inflammatory drugs (NSAIDs) combined with superior gastrointestinal (GI) tolerability. Lumiracoxib (Prexige®) is a novel COX-2 selective inhibitor that has rapid absorption and plasma clearance resulting in a short plasma half-life (3–6 hours) (6). Selectivity for COX-2 over COX-1 has been demonstrated for lumiracoxib both in vitro and in vivo (7) and at doses up to 800 mg in humans (8). Lumiracoxib lacks a sulphur-containing moiety but possesses a carboxylic acid group, which confers weakly acidic properties (pKa 4.7) (9). As a possible consequence of its distinct structure, lumiracoxib rapidly moves into (10) and persists in inflamed tissue in animal models (11), an effect not seen with other COX-2 selective inhibitors tested. In addition, lumiracoxib is associated with sustained higher concentrations in synovial fluid compared with plasma in patients with rheumatoid arthritis (12).

Lumiracoxib has demonstrated efficacy in relieving the chronic pain of OA in knee and hip models. The results of a 4-week, dose-finding study in patients with OA of the hip or knee suggested that lumiracoxib was effective in reducing joint pain intensity, and had a favourable safety profile compared with a traditional NSAID (13). Efficacy in OA was confirmed by two similarly designed 13-week studies, each involving more than 1600 patients with OA of the knee, where lumiracoxib 200 mg and 400 mg od significantly reduced OA pain intensity and improved patient’s global assessments of disease activity compared with placebo from the first assessment visit at 2 weeks through to the study end (14, 15). The superior GI tolerability of lumiracoxib in comparison with NSAIDs was demonstrated in a 13-week study involving 1042 patients with OA, where lumiracoxib was found to have a GI safety profile (assessed in terms of gastroduodenal ulceration by endoscopy) superior to ibuprofen and similar to celecoxib (16).

The aim of this study was to compare the efficacy of lumiracoxib (200 or 400 mg od) with placebo in patients with OA of the hand. Safety and tolerability were assessed as secondary objectives.

Methods

This was a randomized, double-blind, placebo-controlled, parallel-group study, conducted at 52 centres in four countries (Germany, Canada, France and Italy). The study was performed in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki (1964 and subsequent revisions). All patients provided written informed consent prior to any study procedure.

Patients and study design

Patients aged ≥18 years with a diagnosis of symptomatic primary OA of the hand, as confirmed by the American College of Rheumatology classification criteria (4), who had symptoms for at least 3 months were eligible for inclusion. Female patients were required to be post-menopausal, surgically sterile or practising an acceptable method of birth control. Patients with evidence of active peptic ulceration within the previous 12 months, secondary OA, other types of disease in the target hand or other significant medical problems were excluded.

Patients meeting the inclusion criteria

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underwent a washout period of 3–7 days for NSAIDs and/or other analgesic therapy. Physical examinations, evaluation of vital signs and assessment of baseline disease activity were performed before randomization. Patients were required to have pain intensity $\geq 40$ mm on a 100 mm Visual Analogue Scale (VAS) (most pain) in the target hand during the 24 hours prior to baseline. An increase in pain intensity in the target hand of either $\geq 20\%$ or $\geq 10$ mm VAS at the baseline visit compared with screening values (whichever was greater) was required to assess those patients who required analgesia. Patients were randomized in a 1:1:1 ratio to receive lumiracoxib 200 mg od, 400 mg od or placebo for 4 weeks. Rescue medication (paracetamol $\leq 2$ g/day) was permitted during the screening and treatment periods, except from midnight directly before a scheduled study visit. Patients were asked to return all unused medication at the end of the study and were considered to be compliant if they had taken at least 80% of the daily doses.

During treatment, efficacy and safety were assessed during study visits at Weeks 2 and 4, and a follow-up telephone call was made at Week 6 to check for serious adverse events (SAEs). All randomized patients prematurely discontinuing were followed-up by telephone up to 2 weeks after their last known dose of medication in order to request information on the possible occurrence of a complicated ulcer and to ensure a complete dataset. Prespecified criteria for discontinuation due to notable laboratory parameter changes were established.

**Efficacy measures**

The primary efficacy variable was overall OAPain intensity (VAS mm) in the target hand, assessed after 4 weeks of treatment. This was determined by asking patients to indicate the most pain they had from their OA over the previous 24 hours. Secondary efficacy variables were overall OAPain intensity (VAS mm) in the target hand in the previous 24 hours, assessed after 2 weeks of treatment, physician’s and patient’s global assessments of disease activity (VAS mm) at each visit, patient’s functional status measured by the Australian/Canadian OA Hand Index (AUSCAN) categorical score at Week 4, and patient’s QoL measured by the Health Assessment Questionnaire (HAQ$^\circ$) disability dimension at Week 4. Patient’s grip strength was measured by a dynamometer at Week 4 and the use of rescue medication was monitored at Weeks 2 and 4.

The AUSCAN is a validated, self-administered questionnaire developed to assess the functional status of the hand during the previous 48 hours (17). It is based on five-point Likert scales, where numerical values are allocated to each of 5 possible responses (none = 0; mild = 1; moderate = 2; severe = 3; extreme = 4). The AUSCAN questionnaire consists of 15 questions grouped into three sections (Pain = 5 questions; Difficulty Performing Daily Activities [DPDA] = 9 questions; Stiffness = 1 question). The AUSCAN Total score is derived by summation of the scores for the 15 individual questions.

The HAQ$^\circ$ questionnaire disability dimension consists of 22 questions grouped into 12 sections and focuses on the patient’s ability to perform common activities of daily living over the previous 7 days (18). The study nurse or investigator was advised to check patients’ questionnaires for completeness. The dynamometer procedure allowed the patient to make three sequential attempts to measure his or her maximum grip strength. The patient was allowed to rest and recover from the previous attempt before starting the next one.

**Tolerability and safety measures**

All adverse events (AEs) were recorded and assessed in terms of severity (mild, moderate and severe) and suspected relationship to study drug. Safety and tolerability was also evaluated through regular assessment of haematology, blood chemistry and urinalysis. Vital signs and physical examinations were performed at baseline and at Weeks 2 and 4; electrocardiograms (ECGs) were performed at baseline and at Week 4.

**Statistical analyses**

The planned total sample of 498 gave a power of over 80% to detect a significant difference between lumiracoxib 400 mg od and placebo at a 5% level. If this were achieved, significance of lumiracoxib 200 mg od would also be tested at the 5% level without the need to adjust for multiple testing.

The primary efficacy analysis was performed on the intent-to-treat (ITT) population, comprising all randomized patients exposed to study drug. Last observation carried forward (LOCF) was performed in the event of missing observations. The primary efficacy variable was analyzed using an analysis of covariance model fitting baseline value, centre and treatment group. Between–treatment pairwise comparisons were performed using least square means (LSMs) obtained from the model.

The analysis of all secondary efficacy variables was also performed on the ITT population (LOCF). For the analysis of the number of paracetamol rescue tablets taken during the study, treatment groups were compared with respect to the proportion of patients having taken rescue medication using a multiple logistic regression model with country, treatment group and baseline OA pain (VAS mm) as explanatory variables. Odds ratios and 95% confidence intervals were determined. For each of the other secondary efficacy variables, between–treatment pairwise comparisons were performed using LSMS obtained from an analysis of covariance model. The safety and ITT populations were identical. The occurrence of prespecified AEs was summarized and any differences between treatments analyzed using Fisher’s exact test. Prespecified AEs were defined using medical terms as coded by a standard medical dictionary:

- Prespecified GI AEs and ulcers: Abdominal pain not otherwise specified (NOS), abdominal pain lower, abdominal pain upper, abdominal pain aggravated, constipation, constipation aggravated, diarrhea NOS, diarrhea aggravated, nausea, nausea aggravated, vomiting aggravated, dyspepsia, dyspepsia aggravated, dysphagia, dysphagia aggravated, loose stools, oes-
sophageal ulcer, peptic ulcer, peptic ulcer aggravated, gastric ulcer, duodenal ulcer, duodenal ulcer aggravated, gastroduodenal ulcer, GI ulcer, pyloric ulcer.

- Peripheral oedema AEs: Oedema peripheral, oedema lower limb, oedema upper limb, oedema NOS.

- Chest pain AEs: Chest pain not elsewhere classified.

Results

Patients and treatment

Of 669 patients screened, 594 were randomized to receive lumiracoxib 200 mg od (n=205), lumiracoxib 400 mg od (n=193) or placebo (n=196) (Fig. 1). Patient demographics and baseline disease characteristics were comparable between treatment groups (Table I). A slightly smaller proportion of patients in the lumiracoxib 400 mg od group had received prior treatment with NSAIDs compared with the other treatment groups, although this difference was not significant.

Compliance rates were high, with ≥99% of patients in each group achieving >80% compliance over the treatment period. During the course of treatment, 10, 11 and 14 patients withdrew prematurely from the lumiracoxib 200 mg od, lumiracoxib 400 mg od, and placebo groups respectively. Figure 1 illustrates the breakdown of patients screened, randomized, withdrawn and completing the study.

Efficacy

Primary variables. Lumiracoxib 200 mg od and 400 mg od reduced overall OA pain intensity in the target hand compared with placebo at Week 4 (Fig. 2; Table II). Between-treatment comparisons of LSMs showed that lumiracoxib 200 mg od and lumiracoxib 400 mg od were statistically superior to placebo (treatment-placebo differences: -9.9 mm and -10.2 mm for lumiracoxib 200 and 400 mg od, respectively; both p < 0.001). No significant difference was observed between the two doses of lumiracoxib in terms of the reduction in overall OA pain intensity.

Secondary variables. Lumiracoxib was significantly more effective than placebo with respect to overall OA pain intensity in the target hand at Week 2 (treatment-placebo LSM differences: -9.6 mm and -8.4 mm for lumiracoxib 200 and 400 mg od, respectively; both p <0.001). No significant difference was observed between the two doses of lumiracoxib in terms of the reduction in overall OA pain intensity at Week 2.

Mean changes from baseline in overall OA pain intensity in the target hand at Weeks 2 and 4 are shown in Table II. Both doses of lumiracoxib were significantly superior to placebo for patient’s and physician’s global assessments of
disease activity at Weeks 2 and 4 (all p < 0.001). Mean changes from baseline are shown in Table II. Analysis of AUSCAN Total score LSMs at Week 4 showed that lumiracoxib 200 mg and 400 mg od were significantly superior to placebo in terms of patient’s functional status (p=0.003 and p<0.001, respectively) (Fig. 3; Table III). Both doses of lumiracoxib were significantly superior to placebo with respect to all of the AUSCAN sub-scale scores (Pain, DPDA and Stiffness) after 4 weeks of treatment (all p < 0.01) (mean change from baseline shown in Table III).

Both doses of lumiracoxib were significantly superior to placebo in terms of overall rescue medication use: 52.2% of patients in the lumiracoxib 200 mg od group (p=0.035 vs placebo), 43.3% of patients in the lumiracoxib 400 mg od group (p<0.001 vs placebo) and 61.9% of patients in the placebo group required rescue medication. In addition to overall intake, comparison of rescue medication use from baseline to Week 2 and from Week 2 to Week 4 showed a significant difference for both doses of lumiracoxib versus placebo (data not shown). In addition, mean rescue tablet consumption per day was higher in the placebo group than in the active treatment groups. No significant differences between the two doses of lumiracoxib with respect to the amount of rescue medication consumed.

No significant differences were observed between treatment groups in terms of QoL (HAQ® disability dimension) or patient’s grip strength at Week 4.

Table II. Change from baseline in overall OApain intensity in the target hand and patient’s and physician’s global assessments of disease activity at Weeks 2 and 4

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Change from baseline (VAS mm), mean ± SD</th>
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<tbody>
<tr>
<td></td>
<td>Overall OApain intensity in the target joint</td>
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<tr>
<td></td>
<td>Week 2</td>
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<tr>
<td>Lumiracoxib 200 mg od (n=205)</td>
<td>−21.3 ± 19.2</td>
</tr>
<tr>
<td>Lumiracoxib 400 mg od (n=193)</td>
<td>−21.1 ± 21.9</td>
</tr>
<tr>
<td>Placebo (n=196)</td>
<td>−12.5 ± 16.8</td>
</tr>
</tbody>
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OA: osteoarthritis; od: once daily; SD: standard deviation; VAS: visual analogue scale.
No clinically significant treatment-related abnormalities were observed during the study in vital signs, ECG parameters or clinical laboratory measures and no patients discontinued because of abnormal laboratory values.

**Discussion**

The current findings indicate that lumiracoxib is effective and well tolerated for the treatment of OA of the hand. Both doses of lumiracoxib demonstrated significant superiority to placebo in terms of overall OA pain intensity in the target hand after 4 weeks of treatment. No significant difference was observed between lumiracoxib 200 mg and 400 mg od for this variable. These results are consistent with those observed in previous studies, in both a 4-week study involving patients with OA of the hip or knee (13) and two 13-week studies in patients with OA of the knee (14, 15), where lumiracoxib demonstrated significantly superior efficacy compared with placebo in terms of reducing joint pain intensity.

Both doses of lumiracoxib demonstrated significantly superior efficacy compared with placebo in terms of patient’s and physician’s global assessments of disease activity. Use of the validated AUSCAN questionnaire, which has been specifically designed to assess functional improvements in hand OA, demonstrated that treatment with lumiracoxib 200 mg and 400 mg od resulted in significantly superior AUSCAN Total scores compared with placebo at study end. The effect of treatment on aspects of patients’ daily lives relating to their condition, including pain, stiffness and the ability to perform daily activities, were assessed by evaluation of the AUSCAN subscales. Overall, both doses of lumiracoxib were associated with significantly lower Pain, DPDA and Stiffness subscale scores versus placebo at the end of the study. The maintenance of pain relief and improvements in stiffness and manual dexterity is particularly important in patients with OA of the hand, which is considered to be an important indicator of a systemic tendency to OA involving weight-bearing joints, notably the hip and knee (3). Rescue medication use was significantly greater in the placebo group compared with either active treatment group, which may help to explain the reductions in pain intensity and the lack of patients discontinuing due to unsatisfactory therapeutic effect in the placebo group.

No significant differences could be found between treatment groups in terms of patient’s grip strength at Week 4. Of note, it has previously been observed that the results of grip strength assessments may not correlate with...
functional consequences, reducing the value of this measurement (19); an observation confirmed by the findings of this study.

Analysis of QoL was included as an exploratory measure in the study; however, a significant improvement in QoL versus placebo was not observed. Although the HAQ® is a validated tool for measurement of health status (18-20), improvements in QoL are not always evident with NSAIDs which have demonstrated efficacy in other measures of clinical activity (21, 22).

Overall, lumiracoxib 200 mg and 400 mg od were well tolerated with a safety and tolerability profile similar to that of placebo. No dose–response relationship was observed between lumiracoxib 200 mg and 400 mg od for the incidence of AEs. The results provide further support for the good GI tolerability of lumiracoxib as observed previously in an endoscopy study in more than 1000 patients with OA of the hip, knee, hand or spine, which indicated that lumiracoxib causes less gastroduodenal ulceration and fewer GI AEs compared with the traditional NSAID ibuprofen (16).

The results of the current study indicate that lumiracoxib 200 mg or 400 mg od is an effective and well-tolerated treatment option for the management of primary OA of the hand, providing effective pain relief, and improving joint stiffness and overall function. To our knowledge, this is the first clinical study conducted specifically with the primary objective of evaluating the efficacy of a COX-2 selective inhibitor in patients with OA of the hand. The reduction in joint pain and improvements in joint stiffness and functional ability following treatment with lumiracoxib may help to improve dexterity and limit disability in patients with OA affecting the hands (2) and, consequently, could in the long-term, have a positive impact on patients’ QoL and overall well-being.

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Lumiracoxib efficacy in OA of the hand / J.K. Grifka et al.

