Rofecoxib improves quality of life in patients with hip or knee osteoarthritis

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A major goal of osteoarthritis (OA) treatment is pain management to improve function and maximise quality of life. Rofecoxib is a highly selective inhibitor of cyclooxygenase-2 used in symptomatic treatment of inflammation and pain in patients with osteoarthritis of the hip or knee.

Aim: The primary aim of this study was to assess the effects of rofecoxib on quality of life in elderly patients with painful osteoarthritis flares of the hip or knee, who were not responsive to or had adverse reactions to previous NSAID therapy. In addition the switch pattern of NSAIDs in these patients was recorded.

Methods: A 3-week prospective open label multicentre study with rofecoxib 25 mg daily in 134 male and female outpatients with painful osteoarthritis flares of the knee or the hip (mean age 69 years, SD ± 8). On day 1 the patients were all switched from their previous NSAID to rofecoxib, followed by continuous daily treatment with rofecoxib 25mg daily over 3 weeks. On day 21 the patients discontinued daily treatment with rofecoxib and had the choice between either staying on rofecoxib, switching back to their previous NSAID, trying another NSAID or stopping drug treatment. The impact on quality of life was measured by the difference in SF-12 between day 0 and day 21. Further endpoints included changes in self-reported pain, stiffness and functional ability as measured by the WOMAC index (Western Ontario McMaster Universities Osteoarthritis Index). Correlation studies were performed between the WOMAC pain subscale and quality of life as measured by the SF-12 at baseline and over the course of the study. Patients’ report of general health status and overall assessment of pain intensity, as measured by visual analogue scale (VAS), was correlated with physicians’ and patients’ assessment of the efficacy of rofecoxib treatment.

Results: Quality of life improved with rofecoxib: the physical component summary score (SF-12 PCS) was improved by a statistically significant +16.2% (p <0.0001) after 3 weeks, while the mental health component summary score (MCS) was improved by +3.0% (n.s.). Disease-specific symptoms measured by the WOMAC questionnaire were significantly improved under rofecoxib after 3 weeks: pain decreased by 29% (p <0.0001) and stiffness by 25% (p <0.0001), while functional ability increased by 24% (p <0.0001). The improvement in SF-12 PCS correlated negatively with the decrease in WOMAC scores (r = –0.54, p <0.0001; r = –0.46, p <0.0001 and r = –0.64, p <0.0001 respectively). General health was significantly improved by +30.5% (or 15.96 mm, p <0.0001) between baseline and day 21, while pain was significantly reduced by –35.2% (or 17.67 mm, p <0.0001) on the VAS scales. At the end of the 3-week study 75% of the patients and 84% of the treating physicians rated the efficacy of rofecoxib from good to excellent. Two weeks after study end the planned telephone survey revealed that 54% of the patients preferred to stay on therapy with rofecoxib, 19% had decided to switch back to their previous NSAID, 19% had been switched to another NSAID and 7.5% had discontinued treatment. The switch pattern is unknown in the remaining 7.5%.

Conclusion: Rofecoxib significantly improves quality of life, as measured by the SF-12, in OA patients who were either unresponsive to or presented with adverse reactions to previous NSAID therapy (including celecoxib). In addition, rofecoxib significantly improved pain, stiffness and function, as assessed by the WOMAC questionnaire.

Key words: hip osteoarthritis; knee osteoarthritis; rofecoxib; quality of life; SF-12; WOMAC
Introduction

Rofecoxib is a highly selective inhibitor of cyclooxygenase-2 (COX-2), one of the two identified isoforms involved in the biosynthesis of prostaglandins. Rofecoxib is used for symptomatic treatment of inflammation and pain in osteoarthritis (OA).

COX-1 is present in various tissues, i.e. in the stomach, the gut, the kidney and thrombocytes. It has been previously shown that COX-1 is responsible for the prostaglandin-dependent mechanisms of cytoprotection, particularly at the level of the gastrointestinal mucosa and thrombocyte aggregation. Moreover, COX-1 is involved in the process of renal function. Inhibition of COX-1 via non-selective cyclooxygenase inhibitors (generally referred to as non-steroidal anti-inflammatory drugs or NSAIDs) has resulted in the production of gastrointestinal lesions and renal toxicity [1, 2].

COX-2 is constitutively present in few tissues, i.e. the brain and the kidney, and is induced by inflammatory signals. It is generally accepted that COX-2 is mainly involved in the synthesis of prostanoids mediating pain, inflammation and fever. Thus, a selective inhibition of COX-2 results in improvement of these symptoms without producing the typical NSAID-induced gastrointestinal side effects [1, 3, 4].

In clinical studies involving patients with osteoarthritis of the knee and hip, the efficacy of rofecoxib 12.5 mg or 25 mg daily was of the same order of magnitude as diclofenac 50 mg tid or ibuprofen 800 mg tid. Clinically significant improvement of osteoarthritis symptoms, i.e. pain, stiffness and functional disability, was reported. However, the incidence of defined adverse gastrointestinal reactions (gastropathies) was significantly lower with rofecoxib than with the non-selective cyclooxygenase inhibitor diclofenac [5, 6]. Osteoarthritis is the commonest condition affecting the joints and the major source of disability in elderly people. The main symptom of OA is pain, which ranges in severity from mild symptoms with little or no impairment to severe pain with marked incapacity which drastically interferes with daily activities [7]. The consequences of pain are widespread, leading to depression, restricted social life, sleep problems and impaired mental functions [8].

A major goal of OA treatment is therefore pain management to optimise algo-functional features and to improve patients’ quality of life.

Only limited data are available on the relation between therapy with NSAIDs and quality of life. A recent randomised placebo-controlled study assessed the effects of rofecoxib on health-related quality of life (HRQL) with the SF-36 in patients with worsening pain after discontinuation of previous therapy with NSAIDs [9]. The aim of this study was to assess whether rofecoxib would significantly improve quality of life in osteoarthritis patients who were either unresponsive to or presented with adverse reactions to previous NSAID therapy.

Methods

Patients

We screened 136 outpatients, males and females aged 50 or over, with painful osteoarthritis of the knee or the hip according to ACR criteria. 134 were included in the study. Additional inclusion criteria were the following: intake of NSAIDs (including celecoxib) for at least 5 days prior to study entry. Subjects had to have had pain intensity of 40 mm or more on the VAS in the previous 48 hours when walking on a flat surface, be reluctant to continue on previous NSAIDs (including celecoxib) and be willing to change drug treatment. Radiological evidence of OA in the painful joint had to be documented and at least grade II to IV on the Kellgren-Lawrence scale on an X-ray taken within the previous 12 months.

Exclusion criteria were concurrent medical/arthritic diseases which could confound or interfere with the evaluation of efficacy, such as secondary inflammatory arthritis, gout, episodes of acute monoarticular arthritis, isolated patellofemoral disease, a history of acute ligamentous or meniscal injury of the study joint within the previous 2 years, or arthroscopy of the affected knee in the 3 months prior to study entry. Subjects with hypersensitivity to one of the ingredients of rofecoxib or rescue medication, asthma attacks, episodes of urticaria or acute rhinitis after administration of aspirin or other NSAIDs were not included in the study. Severe heart, renal (creatinine clearance <30 ml/min) or liver insufficiency (including increased liver function tests, GGT, ALAT and ASAT 3 times higher than the upper limit of normal range) were exclusion criteria. Subjects with acute or suspected gastrointestinal bleeding, active gastric or duodenal ulcer, ulcer diagnosed endoscopically within the previous 28 days, steroid injection <3 months prior to study start or who had been previously treated with rofecoxib within the last 6 months were excluded.

Study design

This was a prospective open label 3-week multicentre study. On day 0 (visit 1) patients stopped their previous NSAID therapy and started therapy with rofecoxib 25 mg once daily on the following day, day 1. On day 7 the patients returned for an interim visit (visit 2). In the second study phase, day 7 to day 21, patients continued treatment with rofecoxib. On day 21 the final visit took place (visit 3). Thus the total study duration for a patient was 3 weeks. Two weeks after visit 3 or after discontinuation the patient was contacted to check for adverse events and whether he/she was staying on therapy with rofecoxib (fig. 1).

As pain rescue medication all patients included in the study were allowed to take paracetamol 500 mg on demand (i.e. in the event of breakthrough pain) with a maximum dose of 4 g/d. The investigator counted and recorded all returned tablets at each visit (day 7 and day 21).

There were no study-specific restrictions with regard
to prior and concomitant medication and treatments, except that co-administration of NSAIDs (incl. celecoxib) was not allowed during the study period. Low-dose aspirin (≤100 mg/d) was allowed, provided the dosage was not changed during the three weeks’ study period and had been stable during the previous month.

The radiological severity of OA was assessed at day 0 by the Kellgren-Lawrence index. At each visit (day 0, day 7, day 21) the patient rested in a sitting position for 10 minutes prior to monitoring of vital signs. On each visit participants completed the following questionnaires: patient’s global assessment of disease status (100 mm visual analogue scales (VAS), 0 = very well, 100 = very poor) and patient’s global assessment of treatment satisfaction (5-point scale, 0 = poor and 4 = excellent), patient’s assessment of pain when walking on a flat surface (VAS, 0 = no pain, 100 = major pain) [10] and WOMAC LK 3.1 (Western Ontario Mac Master Osteoarthritis Questionnaire [10] and the SF-12 questionnaire (the SF-12 is a condensed form of the SF-36) [11, 12]. Validated Health Survey SF-12 translations from the international quality of life assessment (IQOLA) project were used in this study [13]. The investigator completed the global assessment of disease status (5 point scale, 1 = very well and 4 = very poor) and the response to therapy questionnaires (5 point scale, where 0 = poor and 4 = excellent).

The study was approved by the local ethics commissions (Protocol VIOXX 16022000.E). The clinical trial was conducted under the Good Clinical Practice guidelines of the former intercantonal drug control administration (IKS, now Swissmedic). All patients gave their informed written consent prior to study entry.

Clinical endpoints assessment
Primary endpoint
The primary endpoint was defined as the effects of rofecoxib therapy on quality of life, as measured by the SF-12 between day 0 (visit 1) and day 21 (visit 3).

Secondary endpoints
The secondary endpoints were change in disease-specific symptoms, including pain, stiffness and functional ability measured by the WOMAC questionnaire. Correlation studies were performed between WOMAC pain and SF-12 quality of life at baseline and over the course of the study. In addition we correlated patients’ assessment of general health status and overall assessment of pain intensity as measured by visual analogue scale, as well as physicians’ and patients’ assessment of efficacy and documentation of the switch pattern among NSAIDs. The study nurse filled in the questionnaires for the patients who could not do it themselves (n = 20/134), on the basis of their answers to her reading out the questions.

Tolerability and safety
Spontaneously reported adverse events were recorded throughout the study. Vital signs were monitored at every visit. Laboratory investigations including haematology, blood chemistry and urinalysis were performed at the inclusion visit (day 0) and repeated on a need basis decided by the investigator. For all adverse events the investigator recorded intensity, relation to test drug and any action taken.

Statistical analysis
The statistical analysis of the results was performed in intention to treat (ITT, last observation carried forward) and per protocol using the SAS Statview 5.01 program. The data normality check was done by Kolmogorov-Smirnov testing. Parametric and non-parametric tests were used, depending on the type of data. The WOMAC results were added for each domain (pain, stiffness and functional ability) and the mean was calculated. Subgroup analyses were performed to check for robustness of the results vs. the influence of two potential external confounding factors: study nurse’s assistance vs. non-assistance in filling in the questionnaire, and intake vs. non-intake of paracetamol during the study.

Figure 1
SVIS study design and patient flow during the course of the study.
Results

Out of 136 patients screened, 134 met the inclusion criteria and agreed to participate in the study. The primary diagnosis was hip OA in 23.1% and knee OA in 76.9% of cases. The radiological Kellgren-Lawrence index was II (slight OA) in 22.4% of the patients and III (moderate OA) or IV (major OA) in 54.5% and 23.1% respectively. 32% of study participants were male and the mean age was 69 years (SD ± 8 years) (table 1).

A total of 92 subjects completed the study per protocol. Of the patients who completed the study, 9 were non-compliant and were excluded from the per-protocol analysis (4 who experienced adverse events, 4 who waited for 2 weeks between visit 1 and visit 2 and therefore took rofecoxib for only one week, and one who confused the study drug with the rescue medication). A further 8 were protocol violators (6 were on paracetamol (3) or high-dose aspirin (3) and not on NSAIDs (3) prior to study entry, 1 had acute pain in the hip after TP-arthroplasty which could have interfered with the efficacy evaluation, and 1 was not on NSAIDs for 5 days prior to study entry) and were excluded from the per-protocol analysis. An additional 25 patients had to be excluded from the per-protocol analysis of the SF-12 because, although they were neither non-compliant nor protocol violators, one or more items were missing from their SF-12 questionnaires. All patients (non-compliants, protocol violators and those with missing items in the SF-12) were included in the ITT analysis (n = 134). Finally the NSAID switch pattern was confirmed in the telephone survey in 124/134 patients and remained unknown in 10/134 patients (fig. 1).

SF-12

The physical component summary score (PCS) improved significantly by 5.21 (absolute value) or +16.2% (relative effect) (p <0.0001, fig. 2). This statistically significant increase in PCS scores was confirmed in all subgroups (whether or not the patients filled in the questionnaires themselves and whether or not the patients took paracetamol during the course of the study). In contrast, the improvement in the mental health component summary score (MCS) was only 1.57 (absolute value), +3.0% (relative value) (n.s.).

WOMAC

As assessed by the WOMAC index, pain decreased by 29% (p <0.0001), stiffness by 25% (p <0.0001) and functional ability was increased by 24% (p <0.0001) over the course of the study (fig. 3). This result was confirmed in both subgroups (whether the patient filled in the questionnaire alone or not) and in the per-protocol analysis. SF-12 PCS was negatively correlated with WOMAC pain (r = –0.54, p <0.0001). A negative correlation was also found between PCS and stiffness (r = –0.46, p <0.0001), as well as between PCS and functional ability (r = –0.64, p <0.0001).

General health status and pain

The general health status and pain when walking on a flat surface were evaluated by visual analogue scale (VAS). General health was significantly improved between baseline and day 21 by +30.5% (or 15.96 mm, p <0.0001). Pain was significantly decreased by –35.2% (or 17.67 mm, p <0.0001) between baseline and day 21 (figures 4a and b). These results concerning both general health and pain were confirmed in the per-protocol analysis.
Efficacy of rofecoxib

During this trial the general efficacy of rofecoxib was assessed separately by the patients and the treating physicians. At the end of the study 75% of the patients (101/134) considered the efficacy of rofecoxib as good to excellent. 19% (25/134) rated the efficacy as fair, 4.5% (6/134) as poor. The treating physicians rated the efficacy of rofecoxib as good to excellent in 84% of cases (113/134), as fair in 9% of the patients (12/134) and poor in 2.9% of the patients (4/134) (table 2).

Adverse events

57 patients experienced a total of 111 adverse events during the course of the study. Two events were declared to be definitely, 33 probably, 23 possibly, 31 probably not and 22 definitely not related to the study drug. Seven adverse events were classified as severe, 38 as moderate and 66 as mild. None was considered serious by the investigators.

No severe adverse cardiovascular event or deep vein thrombosis was observed. No hospitalisation or death occurred due to adverse events (table 3).

Compliance

Compliance was assessed by tablet count. 70% (94/134) of the patients took either 20 or 21 tablets over the 3 weeks. 92% (123/134) took at least 17 out of 21 tablets of rofecoxib. No patient took fewer than 12 tablets. 28% (37/134) of patients took no pain rescue medication at all. 22% (29/134) took fewer than 8 tablets of rescue medication; the remainder took more than 8 tablets of paracetamol for the duration of the study.

Switch pattern

Prior to entry into the study 30/134 patients were on celecoxib at a median dose of 400 mg/d, 39/134 on diclofenac at a median dose of 100 mg/d, 23/134 on ibuprofen at a median dose of
800 mg/d and 10/134 were on mefenamic acid at a median dose of 500 mg/d. The 32 remaining patients were taking one of 10 different NSAIDs/analgesics: piroxicam (8), paracetamol (5), naproxen (5), aspirin (4), acemetacin (2), etodolac (2), flurbiprofen (2), meloxicam (2), aceclofenac (1) and nimesulid (1). In the telephone survey two weeks after completion of the 3-week study 54% of patients (73/134) had decided to stay on rofecoxib, 19% (25/134) preferred to switch back to their previous medication (7/30 back to celecoxib, 15/39 back to diclofenac, 2/23 back to ibuprofen, 1/10 back to mefenamic acid), 9% (12/134) had decided to try another NSAID, 7.5% (10/134) had decided to take no medication at all and in the remaining 7.5% (10/134) the switch pattern is unknown (fig. 5).

Table 3

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oedema</td>
<td>10 (7.5%)</td>
</tr>
<tr>
<td>Pain, lower limbs</td>
<td>10 (7.5%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>8 (4.5%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (4.5%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (4.5%)</td>
</tr>
<tr>
<td>Pyrosis</td>
<td>8 (4.5%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (4.5%)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>4 (3.0%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>4 (3.0%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3 (2.0%)</td>
</tr>
<tr>
<td>Others</td>
<td>55*</td>
</tr>
</tbody>
</table>

Total 111 adverse events in 57/134 patients

* Others (≤2 cases each): acne, allergic reaction, aphthosis mouth, bloating, common cold, constipation, cramps, depression, dizziness, double vision, dry mouth, dyspepsia, effusion knee, fall with injury, gastroenteritis, glaucoma, headache, hernia hiatalis, increased bowel movement frequency, inflammation of venous vessel, insomnia, irregular pulse, nightmare, nycturia, palpitations, paradontosis, pneumonia, restlessness, rhinitis, rash, sense of abdominal fullness, sweating, swelling, urinary tract infection.

Discussion

This study documents the benefits of treatment with rofecoxib in terms of the quality of life of osteoarthritis patients who were either unresponsive to previous NSAID therapy or presented with adverse events from previous NSAID therapy (including celecoxib). It documents the fact that within 3 weeks rofecoxib significantly improved quality of life as measured by the physical health component summary score (PCS) of the SF-12. In addition, rofecoxib significantly improved WOMAC pain, stiffness and function over 3 weeks.

Previous studies have demonstrated the efficacy of rofecoxib in the treatment of pain and inflammation due to osteoarthritis and its comparable efficacy profile to classical (non COX-2 specific) high-dose NSAIDs [5, 14–17]. Further studies have demonstrated the superior safety profile of rofecoxib compared to classical NSAIDs, with a particular focus on upper gastrointestinal adverse events (perforation, ulcers and bleeding) [3, 4, 18].

In this study, the SF-12 PCS improved under rofecoxib after 7 days’ therapy and changes over the course of the study attained significance after 3 weeks. The mental health component summary score (MCS) was not significantly improved over the duration of the study. However, the SF-12 MCS has been shown previously to be less responsive, after adjustment for other disease-spe-
Rofecoxib improves quality of life in patients with hip or knee osteoarthritis

One of the secondary hypotheses was that improvement in the WOMAC questionnaire (pain, stiffness and function) correlates with better quality of life in patients with OA. This hypothesis was supported by the documented significant correlations between WOMAC subscales and the PCS SF-12. The positive impact of rofecoxib on WOMAC subscales and PCS SF-12 in patients with painful knee OA increased over the course of the study, supporting gradual symptom improvement by rofecoxib reaching significance within 3 weeks. These results are supported by previously published long-term efficacy data [5, 14–17].

OA is a disease in which compliance and persistence are known to be rather poor. In this study 70% of patients had 100% compliance with rofecoxib over the duration of the study, while the remaining 30% were only partially compliant. However, not a single patient took less than 12 tablets of rofecoxib over the 3 weeks' duration of the study. The telephone survey 2 weeks after study end documented that 54% of the patients included confirmed their decision taken on day 21 to stay on therapy with rofecoxib. Only 19% of patients preferred to switch back to their previous treatment (38% of the diclofenac patients, 23% of the celecoxib patients, 10% of the mefenamic acid patients and 9% of the ibuprofen patients). The physicians’ and patients’ assessment of the efficacy of rofecoxib was recorded to document patient and physician satisfaction with rofecoxib. After 3 weeks of continuous daily treatment with rofecoxib, 75% of patients rated the efficacy of rofecoxib as good to excellent and the treating physicians did so in 84% of their patients. This result is consistent with the observed compliance.

In conclusion, rofecoxib was generally safe and well tolerated, a finding in line with the safety and tolerability profile of rofecoxib described in previous studies [3, 4, 18]. Two patients developed oedema of the lower limbs which the investigators considered to be a severe, although not serious, adverse event. The most common renal effects of conventional NSAIDs attributable to the inhibition of COX are a reduction in glomerular filtration rate (GFR) and reductions in the excretion of sodium, with the attendant potential for fluid retention and oedema. It has been previously shown that the acute (24–48 hours postdose) sodium-retaining effect of 50 mg rofecoxib is comparable to that of the NSAID indomethacin [19]. This effect resolved over the 14 days of treatment with rofecoxib, in contrast to its persistence with indomethacin. In addition, rofecoxib did not significantly affect GFR [19]. Based on their mechanism of action and current clinical evidence, it seems prudent to assume that all NSAIDs, embracing all COX-2 inhibitors including rofecoxib and celecoxib, share the well-known potential for adverse renal experiences leading to water retention and oedema [20].

There are several potential limitations to this study: first, it was an observational study and therefore there was no control group. It is unclear whether a placebo effect of a drug switch in itself has a role in the improvement of symptoms, and the available data is limited. However, the selected patients matched the inclusion criteria, i.e. they were either unresponsive to or presented with adverse events from previous NSAID-therapy (including celecoxib). There are no available data on the NSAID switch pattern of patients treated with NSAIDs. This study confirms that after 3 weeks' treatment some patients switch back to their previous NSAID, while others continue treatment and others prefer to halt it. This 3-week study corresponds to the typical clinical situation where OA flare patients dissatisfied with their previous NSAID therapy are switched to another treatment. Second, the study was of short duration, which is in line with acute OA flare episodes. However, the study was long enough to document rofecoxib's rapid onset of action and its sustained efficacy over 3 weeks. Other studies have documented the long-term efficacy and safety of rofecoxib for a period of up to 52 weeks and were appropriately designed to do so [5, 14, 16, 21]. Third, the study relied on the SF-12 to evaluate quality of life. The SF-12 is a shorter and more convenient form for patients to fill in than the SF-36. This advantage is outweighed by the fact that if single items are missing in one patient the summary score cannot be computed for evaluation. This was the reason why in this study 25 patients (out of 134) had to be excluded from the per-protocol analysis, as SF-12 single data were missing. In addition, nine of these patients were non-compliant. However, this had no impact on the conclusions as the per-protocol and ITT analysis showed comparable results likely to be in relation to the high level of significance. Fourth, the study was too small to assess patient preference for rofecoxib as compared to the other individual drugs used prior to entry into the study. However, in general (i.e. as compared to all other NSAIDs/analgesics used before inclusion) most of the patients documented their preference by deciding to stay on therapy with rofecoxib after study end.

In conclusion, this study confirms that rofecoxib improves quality of life in patients with painful knee and hip OA. In addition, the treatment positively influences disease-specific symptoms, such as pain, stiffness and decreased function, within 3 weeks.

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