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Adverse Events Associated with Rofecoxib Therapy

Results of a Large Study in Community-Derived Osteoarthritic Patients

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Abstract

Objective: To evaluate the safety profile of rofecoxib, a selective cyclo-oxygenase-2 inhibitor, in patients with osteoarthritis who are receiving care in non-hospital practice settings.

Design: All patients participating in a large 24-week, open-label, non-pharmacological intervention trial were given rofecoxib for painful osteoarthritis of the knee or hip. They started at a dose of 12.5mg once daily for the first month, with the option of increasing to 25mg daily thereafter, if needed for efficacy. Adverse events were closely monitored. We considered all adverse events that occurred during treatment and within 14 days of discontinuation of rofecoxib.

Patient Group Studied: 2896 patients (861 males and 2035 females) were involved in the safety analysis. Their mean (SD) age was 66.8 (9.9) years, and 631 patients (21.8%) were aged ≥75 years. There were 913 patients (31.5%) with hypertension and 151 (5.2%) with diabetes mellitus at the start of the study; 78 patients (2.7%) had a prior medical history of angina and/or myocardial infarction. The mean (SD) duration of rofecoxib treatment was 139 (62) days.

Results: A total of 519 patients (17.9%) discontinued rofecoxib. The main reasons for discontinuation were dyspepsia (4.4%), nausea (2.4%) and dizziness (2.1%). The annualised incidence rates (95% CI) of complicated and uncomplicated upper gastrointestinal ulcers, myocardial infarction, and stroke were 1.36 (0.76–2.23), 0.09 (0–0.50) and 0.45 (0.16–1.05), respectively.

Conclusion: This study conducted in conditions close to daily practice confirms that the use of rofecoxib is associated with a low rate of serious adverse events in patients with osteoarthritis.

Double-blind, randomised studies have shown that rofecoxib, a selective cyclo-oxygenase (COX)-2 inhibitor, has equivalent anti-inflammatory and analgesic efficacy to conventional nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of osteoarthritis, but with significantly less gastrointestinal toxicity.[1,2] Based on the results of a meta-analysis of eight phase 2b/3 controlled trials in over 5000 patients with osteoarthritis, the rate of gastrointestinal tract perforations, symptomatic gastroduodenal ulcers, and upper gastrointestinal tract bleeding (PUB) per 100 patient-years was significantly lower with rofecoxib than with nonselective NSAIDs (1.33 vs 2.60, respectively ; relative risk, 0.51; 95% CI, 0.26–1.00).[3] Furthermore, in over 8000 patients with rheumatoid arthritis enrolled in the VIGOR (VIOXX Gastrointestinal Outcomes Research) study, the relative risk of confirmed clinically important upper gastrointestinal events for rofecoxib at twice the maximal therapeutic dose (50 mg/day) versus naproxen at a standard dose (1 g/day) was 0.5 (95% CI, 0.3–0.6; $p < 0.001$).[4] However, it should be argued that clinical trials include selected patients and hence, their findings may not be generalisable to the wider population in which the drug will normally be used.[5] This drawback leads to the need for studies conducted in the postmarketing setting.[5]

Apart from gastrointestinal safety, recent papers dealt with the issue of whether COX-2 inhibitors, including rofecoxib, may be associated with an increased relative risk for thrombotic events in individuals at risk.[6-9]

These features prompted us to report the safety profile of rofecoxib as assessed in a large open-label clinical trial on osteoarthritic patients recruited from community rheumatologists.

Population and Methods

A total of 2957 patients with painful osteoarthritis of the knee or hip were included in a study for which the primary objective was to evaluate the influence of nonpharmacological interventions on the outcome of osteoarthritis.[10] The study was a 24-week open-label trial with a 2×2 factorial design comparing four groups:

- tools
- exercises
- tools and exercises
- no intervention

where tools was a weekly diary, including the recording of pain (100mm visual analogue scale [VAS 0–100]) and disabling activities (Western Ontario and McMaster Universities Osteoarthritis Index physical function subscale [WOMAC]). Patients discussed the data with their rheumatologist at each follow-up visit. Exercises consisted of home-based exercise programmes undertaken daily with the aid of a videotape and booklet.

In this study all the patients received rofecoxib at a starting dose of 12.5mg once daily for the first 4 weeks, with the option of increasing to 25mg once daily thereafter for efficacy. Efficacy outcomes were assessed using a VAS 0–100 pain scale, the WOMAC and a quality of care rating (0–100). Efficacy was assessed only at the end of the study in order to prevent any interference with the evaluation of 'tools'. The secondary objective (which is reported in this manuscript) was the evaluation of the safety profile of rofecoxib. The data for the safety analysis were obtained from a total of 2896 patients. The study was approved by the Institutional Review Board for the Protection of Human Subjects at Cochin University Hospital, Paris, France. Patients entered the study after reading and signing an informed consent form. The study population consisted of outpatients recruited from the practices of French rheumatologists. Its main demographic and clinical characteristics at baseline are presented in table I.

Study Design

Patient were eligible if they met both clinical and radiographic criteria for the diagnosis of osteoarthritis of either the knee or hip. Osteoarthritis was required to be symptomatic for at least 6 months, and joint pain had to be present for at least 14 days during the month prior to screening. As the patients enrolled in the study might have been as-

Table I. Demographic and clinical baseline characteristics of the study population (n = 2896)

Sex (no. [%] women)	2035 [70.3]
Age (y [SD])	66.8 [9.9]
Patients aged ≥75y (no. [%])	631 [21.8]
Co-morbidities (no. [%])	
clinical gastrointestinal events	56 [2]
hypertension	913 [31.5]
diabetes mellitus	151 [5.2]
History of angina and/or myocardial infarction (no. [%])	78 [2.7]
Concurrent low-dose aspirin (no. [%])	26 [0.9]

signed to perform an exercise programme, those with a recent history of myocardial infarction were excluded, as were patients with severe co-morbidities (neoplasia, infectious disease, unstable metabolic or cardiovascular disease, connective-tissue disease). The patients with an obvious contraindication to rofecoxib use (known hypersensitivity to the drug, active gastrointestinal disease, severe hepatic or renal disorder) were also excluded. Whatever their treatment group, the patients were given rofecoxib at a starting dose of 12.5mg once daily for the first 4 weeks, with the option of increasing to 25mg once daily thereafter, if needed for efficacy.

Safety Assessment

The protocol included four study visits. In addition to the screening visit, patients were seen at weeks 4, 12 and 24. Adverse events were monitored at each trial visit. Safety assessment consisted of inquiries regarding any sign or symptom that a patient may have experienced, and physical examinations at each visit. Further investigations, including clinical laboratory tests and upper gastrointestinal endoscopy were performed on demand. Adverse events were defined according to the WHO.[11] They included any untoward medical occurrence that was present during treatment, but which did not necessarily have a causal relationship with this treatment.[11] If a relationship between an adverse event and rofecoxib was suspected and at least plausible, then an adverse drug event was assumed.[12] We considered all events that occurred during treatment and within 14 days of discontinuation of rofecoxib. It was assumed that patients would contact their doctor if any serious event occurred after week 24.

Results

The patients were receiving rofecoxib therapy for a mean (SD) period of 139 (62) days, with a median of 169 days (range: 2–284 days). The durations of rofecoxib use were similar across the treatment groups (tools and/or a home non-supervised exercise programme or usual care) and across patients with osteoarthritis of the knee and hip. The daily dosage of rofecoxib was increased to 25mg in 773 patients at week 4 and in 1035 patients at week 12.

Overall Tolerability

A total of 1362 patients (47.0%) reported at least one untoward event during the study, and 888 patients (30.7%) were identified as having experienced at least one adverse event that was probably or possibly related to rofecoxib therapy. A total of 519 patients (17.9%) discontinued rofecoxib because of any event. The main reasons for discontinuation were dyspepsia (4.4%), nausea (2.4%) and dizziness (2.1%). The data are summarised in table II. The time to withdrawal for adverse events is shown in figure 1.

Selected Adverse Events

A total of 15 nonfatal PUB and five nonfatal occlusive arterial events (all stroke) was recorded. Furthermore, a 71-year-old male patient with a history of myocardial infarction and coronary angioplasty, associated with various co-morbidities (angina, type 1 diabetes mellitus, hypertension and hypercholesterolaemia) experienced myocardial infarction while taking rofecoxib for 2 months. At that time, the daily dosage of rofecoxib was 25mg. The drug was stopped, and the patient underwent triple coronary bypass surgery 2 days later. He died as a result of postsurgical complications. The

Table II. Most commonly reported adverse events in the study population (n = 2896)

	No. of adverse events (%)	No. of adverse drug events (%)	No. of withdrawals (%)
Any event	1362 (47)	888 (30.7)	519 (17.9)
Diarrhoea	140 (4.8)	116 (4)	56 (1.9)
Dizziness	115 (4)	93 (3.2)	60 (2.1)
Dyspepsia	289 (10)	258 (8.9)	128 (4.4)
Headache	78 (2.7)	67 (2.3)	43 (1.5)
Hypertension (exacerbation)	94 (3.2)	77 (2.7)	43 (1.5)
Mucocutaneous disorders	129 (4.5)	94 (3.2)	47 (1.6)
Nausea	145 (5)	121 (4.2)	69 (2.4)
Oedema	92 (3.2)	82 (2.8)	51 (1.8)
Somnolence	71 (2.5)	65 (2.2)	20 (0.7)
Weight gain	82 (2.8)	67 (2.3)	19 (0.7)
Others	316 (10.9)	272 (9.4)	105 (3.6)

events are summarised in table III. Overall, the annualised incidence rates of PUB, myocardial infarction and stroke were 1.36 (95% CI, 0.76–2.23), 0.09 (95% CI, 0–0.50) and 0.45 (95% CI, 0.16–1.05), respectively.

Regarding mucocutaneous disorders, there were four serious events requiring inpatient hospitalisation or resulting in significant disability. They consisted of dry mouth, corneal ulceration, venous leg ulcer and allergic rhinitis. The last mentioned was the only one that was assumed to be an adverse drug event.

Discussion

Our study included community-derived osteoarthritic patients, and it was conducted in conditions approximating the daily rheumatology practice. Accordingly, our patients appear fairly representative of the population in which rofecoxib is usually prescribed inasmuch as at the time of the present work, rofecoxib was only approved for the symptomatic relief of osteoarthritis in France.[2] Since all patients enrolled in our study were given rofecoxib, our study population may be considered as an uncontrolled prospective cohort study, which is recognised to be suitable for measuring the occurrence of specific events rather than adverse drug events.[5] Therefore, the primary purpose of this study was to determine the frequency of untoward events that occurred during treatment and within 14 days of discontinuation of rofecoxib regardless of the causal relationship to study drug. In view of the absence of a control group, we will interpret our data by referring to the background frequencies of specific events and results of published clinical studies although it may be hazardous to compare raw event rates across multiple studies. There was another limitation in this study. Except for angina and myocardial infarction, the past history of the study population was not assessed and only clinically significant co-morbidities at entry to the study were recorded.

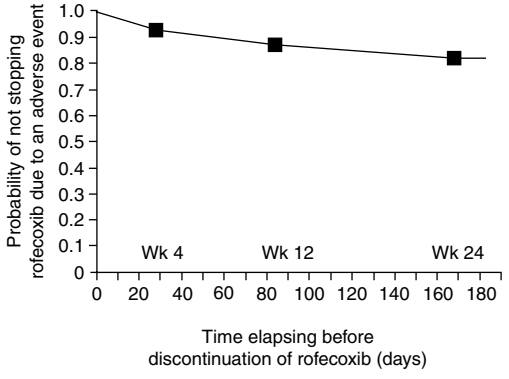

Fig. 1. Time to withdrawal as a result of adverse events in a 24-week study of 2896 patients receiving daily dosages of rofecoxib 12.5 or 25mg.

The proportions of patients who experienced any medical untoward event (47.0%) or adverse drug event (30.7%) in the present study would appear to be high, but they are in line with those usually reported in controlled clinical trials. For instance, the incidence of any clinical adverse experiences ranged between 84–86.2% in patients with osteoarthritis receiving rofecoxib (12.5 or 25mg daily), or diclofenac (150mg daily) for 52 weeks in a double blind randomised trial.[13] Furthermore, withdrawals for untoward events were similar in our study (17.9%) compared with the aforementioned controlled clinical trial (14–27.4%).[13]

The most frequently reported untoward events in our study were subjective functional symptoms. As expected, these were to a great extent gastrointestinal in nature. A substantial number of patients reported a variety of central nervous system symptoms, especially dizziness, headache and somnolence. Finally, the tolerability profile of rofecoxib in our study population appears similar to that observed in previous controlled clinical trials.[2]

Rofecoxib, even at supratherapeutic dosages, has been shown to be associated with a significantly lower incidence of PUB than conventional NSAIDs.[1-4] In the current study, there were four episodes of symptomatic gastroduodenal ulcers and 11 upper gastrointestinal tract bleedings, resulting in an annualised incidence rate of PUB of 1.36 (95% CI, 0.76–2.23). These data are quite comparable with those reported in patients with osteoarthritis receiving rofecoxib during phase 2b/3 controlled clinical trials (1.33 per 100 patient-years)[3] and during the VIGOR study (2.1 per 100 patient-years).[4] In this respect, the present study adds some indirect evidence that the use of rofecoxib is associated with few severe upper gastrointestinal adverse events.

It has been suggested that COX-2 selective inhibitors may increase the risk of cardiovascular thrombotic events.[8] The platelet-vascular homeostasis is mediated by a balance between platelet produced thromboxane A_2 (TxA_2) and endothelial cell-derived prostacyclin (PGI_2). TxA_2 is a vasoconstrictor and promotes platelet aggregation, whereas PGI_2 exhibits opposite properties. PGI_2 is thought to be part of a homeostatic defence mechanism that limits the consequences of platelet activation *in vivo*.[6] Platelet TxA_2 synthesis is regulated by the action of COX-1, whereas COX-2 plays an important role in the increase in PGI_2 formation that occurs in clinical syndromes of platelet activation.[6] In contrast to conventional NSAIDs which inhibit both COX-1 and COX-2, selective COX-2 inhibitors may cause an imbalance between TxA_2 and PGI_2 which may result in thrombosis in patients who are already at increased risk because of the underlying conditions.[6] In fact, arterial thrombosis has been reported after the initiation of celecoxib therapy in four patients with lupus anticoagulants.[14] Moreover, myocardial infarctions occurred in 0.4% of rofecoxib and 0.1% of naproxen recipients in the VIGOR study (95% CI for the difference, 0.1–0.6; relative risk 0.2, 95% CI, 0.1–0.7).[4] However, 38% of patients who had a myocardial infarction met US FDA criteria for the use of aspirin as secondary prophylaxis but were not taking low-dose aspirin therapy.[4] When these patients were excluded from the analysis, the rate of myocardial infarction was not significantly different between the groups.[4] Conversely, the incidence of cardiovascular adverse events that was observed in the rofecoxib osteoarthritis development programme was similar in the rofecoxib treatment group (n = 3357), the combined traditional NSAID group (n = 1564) and the placebo group (n = 711).[15] The incidences of Anti-Platelet Trialists' Collaboration (APTC) end-

Table III. Serious upper gastrointestinal and thrombotic arterial events (n = 2896)

Event	Number
Upper gastrointestinal events	15
symptomatic gastroduodenal ulcers	4
bleeding	11
perforation	0
Thrombotic arterial events	6
myocardial infarction	1
stroke	5

points combining: (i) cardiovascular, haemorrhagic, and unknown death; (ii) myocardial infarction; and (iii) cerebrovascular accident, were assessed in trials comparing rofecoxib with nonselective NSAIDS, and in comparisons of rofecoxib with placebo.[15] In trials comparing rofecoxib with nonselective NSAIDS, incidences of 0.96/100 and 1.42/100 patient-years, respectively, were reported; in trials comparing rofecoxib and placebo the rates were 1.36/100 and 1.93/100 patient-years, respectively. Even if we consider the upper limit of the 95% CI of the annualised incidence rate of arterial thrombotic events, our data tend to confirm these findings. Furthermore, the annualised thrombotic cardiovascular event rate observed in the present study is comparable with that found in controls from four randomised controlled trials of aspirin for primary prevention (weighted mean: 0.92%; range, 0.67–1.71%).[16]

In summary, our study is consistent with a lack of excess of cardiovascular thrombotic events in patients with osteoarthritis receiving rofecoxib 12.5–25mg daily. However, it must be kept in mind that selective COX-2 inhibitors do not affect platelet aggregation. Thus patients for whom low dose aspirin (or warfarin) is indicated to offset known thrombotic risk should certainly continue this therapy if a selective COX-2 inhibitor is introduced.[7] Further studies are required to evaluate the true safety profile of such a combination.[9]

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