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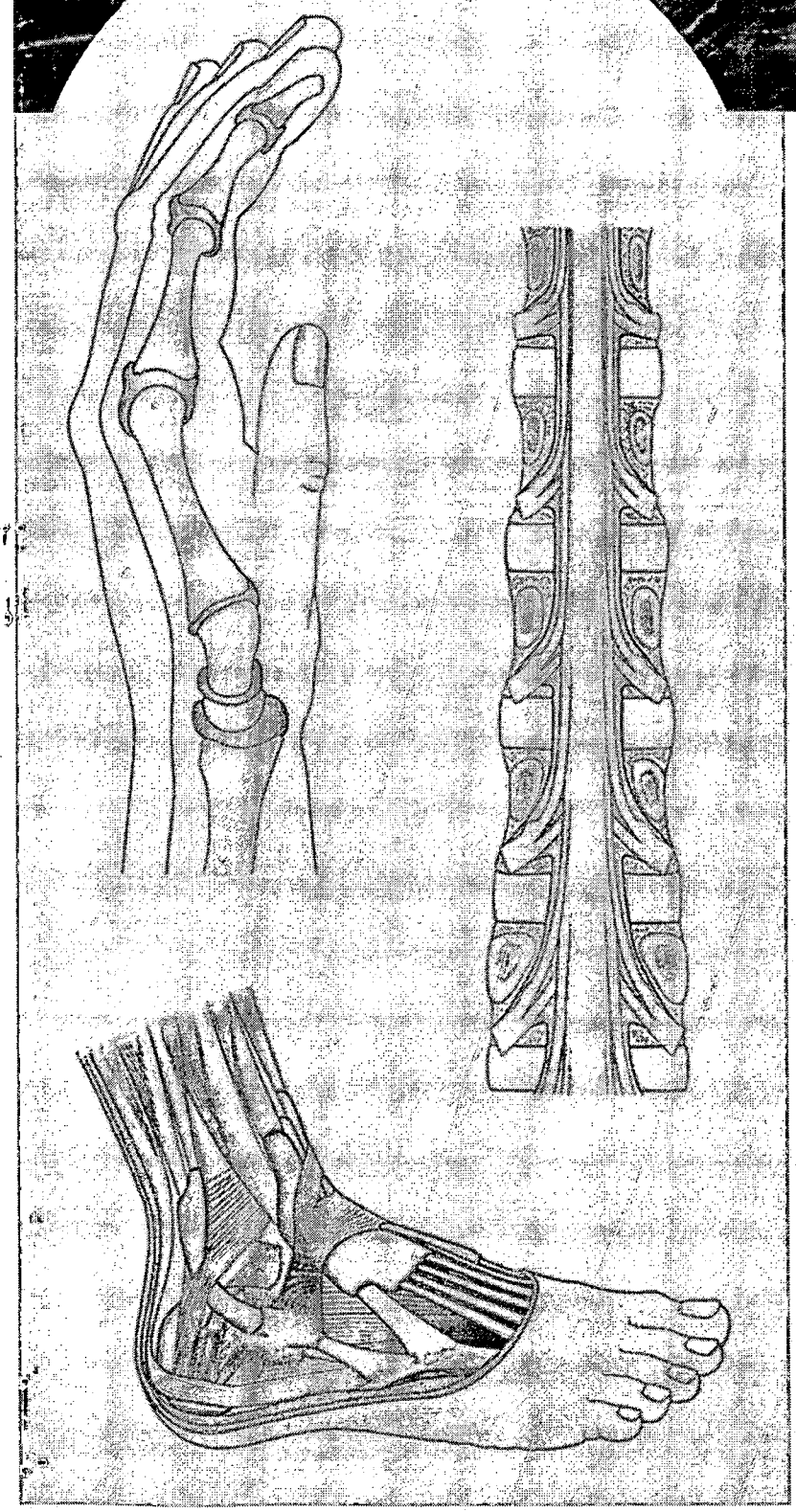

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WELCOME LETTER

Our first review article in this issue of the Australasian Journal of Bone and Joint looks at the gastrointestinal tolerability of a bisphosphonate. The article evaluates several randomised controlled trials involving thousands of patients and points out that there is little or no difference between alendronate and placebo in terms of an increase in upper GI events. It goes on to argue that in the context of the consequences of osteoporosis and its devastating effect on the quality of life, the risks of upper GI effects are low compared to the benefits.

We continue the theme of GI tolerability and safety in another review article, this time looking at some of the data that might help determine therapeutic decisions in patients with osteoarthritic pain who may also be at risk for cardiovascular disease and or/GI complications. The article examines choices of coxibs, NSAIDs and aspirin for analgesic and anti-inflammatory treatment and cardiovascular prevention in patients with different levels of risk.

We also bring you highlights from two recent conferences: the European Congress of Rheumatology held in Lisbon in June, and the 1st Joint Meeting of the International Bone and Mineral Society for Bone and Research which took place in Osaka, Japan, in the same month.

And finally, don't forget the Great Australian Bush Bash on Saturday 16 August at Darling Harbour to raise support for Medical Research Fellowships at the Institute of Bone and Joint Research at the Royal North Shore Hospital. The organisers promise a spectacular evening of wining, dining, bush dancing, side shows, sheep shearing, riding the bucking mechanical broncho and playing games of skill and chance. For more information, call the organisers (02) 9926 7399 or e-mail sambrook@med.usyd.edu.au.

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CONTENTS

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Moderate to severe migraine pain relief

Results of a new study presented at the American Academy of Neurology Annual Meeting earlier this year, show that rofecoxib (25 mg once daily and 50 mg once daily) relieves acute moderate to severe migraine pain within two hours, with pain relief extending out to 24 hours in approximately one-third of patients.

The placebo-controlled, double-blind, multi-centre study of 557 patients with acute migraine, randomised patients to take rofecoxib 25 mg (n = 183), rofecoxib 50 mg (n = 192) or placebo (n = 182) once daily.

The primary endpoint of migraine pain relief (mild or no headache pain) at two hours after dosing was experienced by 54% of patients on rofecoxib (25 mg), 56.7% of patients on rofecoxib (50 mg) and 34.3% of patients on placebo; $p < 0.001$ for both comparisons. The 50-mg drug dose was also found to provide statistically more patients with headache relief compared with placebo at 30 minutes ($p = 0.026$), and the 25-mg dose provided more pain relief at one hour compared with placebo ($p < 0.001$).

Rofecoxib was also found to provide more pain relief at 24 hours after dosing compared with placebo. At 24 hours, 33.5% of patients on the 25-mg dose had sustained headache relief, while 37.5% of patients on the 50-mg dose had pain relief, compared with 17.1% on placebo; $p < 0.001$. Other measures of efficacy such as use of rescue medication, sensitivity to light and sound were also improved with rofecoxib compared with placebo.

[Rofecoxib is not indicated in Australia for the treatment of migraine pain.]

Two-fold greater increases in BMD at 12 months

Results from the Efficacy of FOSAMAX versus Evista Comparison Trial (EFFECT) showed significantly greater increases in bone mineral density (BMD) of the lumbar spine and total hip following one-year treatment with once-weekly Fosamax (alendronate sodium) compared to once-daily Evista (raloxifene). The study was the first head-to-head trial comparing alendronate sodium 70 mg once-weekly and raloxifene 60 mg once-daily, in 456 postmenopausal women with osteoporosis.

The preliminary results were presented at the 51st Annual Meeting of the American College of Obstetricians and Gynecologists (ACOG), 26–30 April, by Dr Risa Kagan, co-medical director, FORE-Foundation for Osteoporosis Research and Education, California, USA.

The primary endpoint of the study (percent change in BMD at the lumbar spine after one year) showed more than a two-fold increase in BMD at the lumbar spine in patients receiving alendronate once-weekly as compared to patients receiving raloxifene (4.4% and 1.9%, respectively; $p < 0.001$).

Results for the secondary endpoint (BMD at the hip) showed that alendronate significantly increased BMD at the hip to a greater extent than did raloxifene. Bone mineral density at the hip trochanter significantly increased 3.2% for patients treated with alendronate versus 1.8% for patients on raloxifene at 12 months; $p < 0.001$. Total hip BMD increased 2.0% for patients taking alendronate versus 1.0% for patients on raloxifene at 12 months; $p < 0.001$. Data for BMD of the lumbar spine and total hip also showed significant increases with alendronate compared to raloxifene at the six-month data point.

At 12 months, the percentage of patients maintaining or increasing BMD at the lumbar spine was greater for alendronate (94%) than for raloxifene (75%). While alendronate also resulted in greater reductions in bone turnover markers at six and 12 than occurred with raloxifene.

Benefits of combination therapy in osteoporosis

Patients can experience a greater increase in density (BMD) at one year by using both raloxifene and alendronate together, compared to either drug alone.

Dr Glenn Braunstein, Professor of Medicine, University of California, reviewed the results of a head-to-head study at the Annual Session of the American College of Physicians, 3–5 April 2003.

The study tested a combination of the two osteoclastic bone resorption inhibitors for one year. The 133 postmenopausal women with osteoporosis were randomised to raloxifene, alendronate, a combination of the two, or placebo at doses of 60 mg/day for raloxifene and 10 mg/day for alendronate.

Femoral neck BMD increased by 3.7% with the two drugs combined, at one year, compared to increases of 2.7% for alendronate alone ($p = 0.02$) or 1.7% for raloxifene alone ($p = 0.001$). Lumbar spine BMD increased by 5.3%, 4.3%, and 2.1% from baseline for the combination, alendronate alone, and raloxifene alone, respectively (not statistically significant), and for all three groups, markers of bone resorption decreased within 30 days.

The study authors concluded that raloxifene and alendronate together decreased bone resorption more than either drug alone. A remaining question is whether the BMD data advantage of combining the drugs will translate into a reduction of incidence of fractures.

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Original article

Diagnostic usefulness of routine Lyme serology in patients with early inflammatory arthritis in nonendemic areas

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Abstract

Objective. – To evaluate the diagnostic usefulness of routine Lyme serology in patients who live in nonendemic areas and present with early inflammatory joint disease.

Methods. – All patients admitted to a rheumatology department of a nonendemic area of France for evaluation of joint disease with onset within the last year. The evaluation included a medical history, a thorough physical examination, an electrocardiogram, and an ELISA for antibodies to *Borrelia burgdorferi*.

Results. – We included 90 patients, 51 women and 39 men, with a mean age of 48.1 ± 17.9 years. Mean duration of joint symptoms was 4.3 ± 4.3 months, with a median of 3 months. A patient (1.1%) reported a tick bite and no patients had a history of erythema migrans. Lyme serology was negative in all 90 patients.

Conclusion. – These results do not support routine Lyme serology in patients living in nonendemic areas and presenting with early inflammatory joint disease. However, Lyme serology remains appropriate in patients with features suggestive of Lyme disease. Given that Lyme disease is amenable to curative treatment, a larger study is in order to confirm our findings.

Keywords: Arthritis; Polyarthritis; Lyme disease; *Borrelia burgdorferi*; Diagnosis

The optimal combination of investigations for evaluating early inflammatory joint disease is not agreed on, and wide variations exist in the investigations ordered by rheumatologists [1].

Lyme disease is a multiorgan infection communicated to humans by tick bites [2]. The causative organism is *Borrelia burgdorferi* in most cases, although other *Borrelia* species have been incriminated in Europe. Chronic erythema migrans is the typical but not invariable initial symptom. A variable combination of neurological, cardiac, dermatological, and articular symptoms can occur subsequently [2]. Accurate data on the rate of occurrence of arthritis in Europe are not available. Monoarthritis, usually of knee, and oligoarthritis are the most common patterns. However, polyarthralgia (particularly early in the disease), polyarthritis, and fibromyalgia-like syndromes have been reported [3].

Whether routine Lyme serology is useful in patients with early inflammatory joint disease remains unclear. Berglund et al. [4] reported that Lyme disease was not exceptional among patients presenting with arthritis and living in an area of high endemicity. Limbach et al. [5] obtained similar findings in patients with monoarthritis or oligoarthritis living in an endemic area. Others have recommended that, in endemic areas, Lyme serology should be reserved for patients with a history of exposure [6]. Finally, studies in regions of low endemicity suggest that Lyme serology may be appropriate only in patients with suggestive clinical manifestations [7,8]. The duration of inflammatory arthritis in these studies varied widely but often exceeded several years. Thus, the results may not apply to patients with early inflammatory joint disease.

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The objective of this study was to evaluate the usefulness of routine Lyme serology in establishing the diagnosis of early inflammatory joint disease in patients living in a nonendemic area.

1. Methods

1.1. Patients

All patients who underwent evaluation of early inflammatory joint disease, as inpatients in a rheumatology department located in a nonendemic area of France, between April 1996 and April 2000, were included in the study, provided they resided in that area. "Early inflammatory joint disease" was defined as onset within the last year of monoarthritis, oligoarthritis, polyarthritis, or polyarthralgia with an inflammatory time pattern.

1.2. Evaluation

A detailed medical history was obtained from each patient. Patients were asked about prior tick bites or erythema migrans. A thorough physical examination was performed, with special attention to dermatological, cardiological, and neurological manifestations, potentially suggestive of Lyme disease. The following investigations were performed routinely: electrocardiogram, erythrocyte sedimentation rate and serum C-reactive protein level, an immunoenzymatic assay for IgM rheumatoid factors, and an indirect immunofluorescent assay on Hep-2000 cells for antinuclear antibodies (cutoff, 80). Finally, an ELISA (Méridian, Nice, France) for antibody to *B. burgdorferi* was done routinely. This ELISA uses a mixture of antigens from *B. burgdorferi stricto sensu* (genogroup I) and *B. afzelii* (genogroup III), from Switzerland (strain IRS) and Germany (strain VS 461), respectively. Its high sensitivity makes it an excellent test for screening. However, since its specificity is limited, sera positive by ELISA were to be confirmed by western blot.

2. Results

Ninety patients were included, 51 women and 39 men, with a mean age of 48.1 ± 17.9 years (range 15-84 years). The presenting manifestation was inflammatory polyarthralgia in 37 patients, monoarthritis in 13, oligoarthritis in 11, and polyarthritis in 29. Mean duration of the joint symptoms was 4.3 ± 4.3 months, and median duration was 3 months. One patient had a high-risk occupation. A patient (1.1%) reported a history of tick bites, and none remembered skin lesions consistent with erythema migrans. None of the patients had dermatological or neurological manifestations suggestive of Lyme disease, and none had an atrioventricular block. The erythrocyte sedimentation rate was elevated (>10 mm/h) in 59 patients (65.6%) and the C-reactive protein level was high (>5 mg/l) in 51 patients (56.7%). Findings were positive from tests for rheumatoid factors in 15 patients (16.7%) and for antinuclear antibodies in 42 patients (46.7%).

The ELISA for Lyme disease was negative in all 90 patients (0%, 95% confidence interval by the exact binomial method, 0-4%). Consequently, no western blot tests were done. The final diagnosis was made at discharge or at the first postdischarge outpatient visit, based on clinical findings, results of investigations, and the short-term course. This diagnosis was rheumatoid arthritis in 15 patients, spondyloarthropathy in 16 patients, systemic lupus erythematosus in six patients, polymyalgia rheumatica in five patients, crystal deposition disease in four patients, miscellaneous diseases in 14 patients, and unclassifiable joint disease in 30 patients.

3. Discussion

In this study, Lyme disease serology performed routinely in patients with early inflammatory joint disease living in a nonendemic area was consistently negative.

Antigenic variants are common among *Borrelia* and unevenly distributed across genogroups, geographic areas (with greater diversity in reaction profiles in Europe than in the US), and bacterial proteins. Thus, reactivityof a European serum can depend in large part on the source of the antigens used in the test. The sensitivity of testing varies with the nature and number of antigens used, particularly in Europe. These considerations prompted us to use an ELISA based on antigens from two European strains not yet affected by antigenic drift. The test did not include antigens from *B. garinii*. To our knowledge, no ELISAs including *B. garinii* antigens are licensed for use in France.

Our study has two main limitations. First, patients with any pattern of inflammatory joint disease were included, although the joint manifestations of Lyme disease usually consist in monoarthritis or oligoarthritis [5,7,8]. Our decision to include patients with polyarthritis was based on reports of polyarticular involvement in Lyme disease [7], sometimes mistaken for rheumatoid arthritis [2]. However, polyarticular involvement seems more common in chronic Lyme disease. Furthermore, limiting our study population to patients with monoarthritis or oligoarthritis would not have allowed us to answer the question of our study. We believe this question was worthwhile: in a recent study conducted by the Rheumatic Diseases and Inflammation Group of the French Society of Rheumatology to evaluate practices by presenting a random sample of French rheumatologists with fictional cases, 13% of participants indicated that they would obtain a serological test for Lyme disease to investigate recent-onset polyarthritis without extraarticular manifestations (as compared to only 2% for polyarthritis highly suggestive of rheumatoid arthritis) [1]. Finally, our decision to include patients with inflammatory polyarthralgia may seem open to criticism. However, the sensitivityof physical examination for detecting arthritis is limited and varies with the experience of the physician, and modern imaging techniques have shown that arthritis in patients classified clinically as having arthral-

gia [9]. In our study, analysis of the subgroup of patients with monoarthritis or oligoarthritis provided results similar to those from the overall population, albeit with limited statistical power.

The second major limitation to our study is that we did not use polymerase chain reaction technology to amplify the *B. burgdorferi* genome as a means of diagnosing Lyme disease. It has been shown that negative serological tests do not entirely rule out Lyme disease [3]. However, PCR testing for *B. burgdorferi* would hardly be acceptable as a screening test in low-endemicity areas, particularly as it can be performed only on joint fluid, skin, or cerebrospinal fluid. PCR should be reserved for patients with features suggestive of Lyme disease.

Our results do not support routine Lyme disease serology in patients presenting with recent-onset inflammatory joint disease and living in nonendemic areas. However, this conclusion does not apply to patients with features suggestive of Lyme disease. In our series, a patient reported having been bitten by a tick, and none remembered skin lesions consistent with erythema migrans. Furthermore, none had an atrioventricular block or neurological abnormalities consistent with Lyme disease.

Furthermore, when interpreting our results, it should be borne in mind that the usefulness of a routine diagnostic test depends in part on the consequences of making (or missing) the diagnosis. Lyme disease can be effectively treated and, if untreated, can cause long-term systemic complications. Thus, a low-yield diagnostic test may be acceptable, particularly in patients whose arthritis remains unexplained after the first set of investigations, as was the case for one-third of our patients. We believe that the present studydoes not have sufficient statistical power to provide a definitive answer to the question asked, and that larger studies conducted in other geographic areas are in order. Until such studies become available, and in the subgroup of patients with monoarthritis/oligoarthritis or with unexplained arthritis, serological testing for Lyme disease remains legitimate in nonendemic areas.

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Alendronate and upper GI tract problems: Assessing the evidence

In order for patients with osteoporosis to decrease the risk of fractures, long-term treatments that increase and maintain bone mineral density (BMD) are necessary. And, since osteoporosis is a disease that predominantly affects older people who often have comorbidities and take concomitant medications, there is a greater requirement for agents to be safe and well tolerated over this extended period.

The use of disphosphonate drugs on osteoporosis is well accepted due to its efficacy in preventing bone fracture. Research is also emerging illustrating its good tolerability.

Following its absorption in the gastrointestinal (GI) tract, the oral bisphosponate alendronate (Fosamax®) binds rapidly to sites of bone remodelling (particularly osteoclasts), where it inhibits bone resorption, effectively increasing bone density and decreasing turnover. It is in these two tissues, the GI tract and bone mineral, that exposure to clinically relevant concentrations of the drug occurs, and therefore it is also here that pharmacological effects are anticipated.

A review by Cryer and Bauer recently evaluated the evidence of possible associations of bisphosphonate use with adverse events in the upper GI tract. Their study examined data from published articles and abstracts relating GI adverse events or endoscopy findings to treatment with oral bisphosphonates. The evidence from the studies was rated according to the evidence-based medicine hierarchy, which rated data from randomised controlled trials as the highest level of evidence; the type of end point used; as well as the methodological quality of the randomised controlled trials included.

Initial concern led to guidelines

When bisphosphonates were first introduced, there was some concern about the incidence of oesophagitis reported in patients. This was understood to be largely due to pills becoming stuck in the upper GI tract, or reflux when the patient lies down following administration. These cases led to the development of dosing instructions that minimised the contact of the medication with the oesophagus. Fosamax® alendronate prescribing information recommends: {APPCo PI}

- Fosamax must be taken at least 30 minutes before the first food, beverage, or medication of the day with plain water only. Other beverages (including mineral water), food and some medications are likely to reduce the absorption of Fosamax.
- Fosamax should only be swallowed upon arising for the day with a full glass of water and patients should not lie down for at least 30 minutes and until after their first food of the day. Fosamax should not be taken at bedtime or before arising for the day.

Administering alendronate with plain water assists in fast clearance from the oesophagus, while avoiding food or other beverages prevents alendronate from binding to these substances, which can reduce absorption. By the risk of gastro reflux is reduced if the patient refrains from lying down for 15 mins.

Following the widespread dissemination of the correct dosing instructions, there was a rapid decrease in the monthly rate of reported adverse events, which subsequently has not increased despite the introduction of weekly dosing, and increases in the number of patients being treated.

Dosing recommendations

Alendronate is recommended for the treatment or prevention of osteoporosis. The recommended dosage for treatment is one 70-mg tablet once weekly or one 10-mg tablet once daily. For the prevention of osteoporosis in postmenopausal women, the recommended dosage is 5 mg once per day. {APPCo PI Fosamax} In patients with Paget's disease of bone, alendronate is recommended once per day at a dose of 40 mg, for six months.

Epidemiological studies

The prevalence and incidence of upper GI tract symptoms (including peptic ulcers and bleeding) increase with age and are noteworthily high among older women. Some epidemiological evidence indicts that in women 65 to 74 years of age, the prevalence is approximately 23% for dysphagia, 40% for heartburn and 41% for acid regurgitation. Some patients are at an even greater risk of GI tract adverse events, including patients with a history of GI tract problems and also older patients who often have health characteristics such as NSAID use. The presence of such characteristics in many people, including those participating in trials, means that epidemiological studies that seek to determine GI events in osteoporosis patients need to carefully randomise patients to account for these exacerbating factors.

A large epidemiological study of 49,384 patients examined the risk of hospitalisation for gastric or duodenal perforations, ulcers and bleeds (PUBs). This study showed that patients with osteoporotic fractures who were not taking alendronate had a higher incidence of hospitalisations for PUBs than those without fractures. In a subset of women aged 60 years or more, the incidence of PUBs was similar among patients who had suffered from osteoporotic fractures regardless of their use, or not, of alendronate. {Donahue} {Cryer}

Endoscopy studies

No study that has used endoscopy to evaluate

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oesophageal lesions before, during and after alendronate therapy has detected an increase. With respect to endoscopic detection of gastric and duodenal lesions and the association with alendronate, there have been some conflicting results, although the importance of these results has been somewhat clouded by methodological problems in the study design, such as a lack of placebo, short duration, few patients and lack of double blinding.

One study has reported a significant difference in the endoscopically detected rate of gastric erosion or ulcers in patients using alendronate vs risedronate. An interesting observation of the study was that approximately half the patients who had ulcers identified at day eight in the alendronate group, did not have ulcers at day 15, despite continued use of alendronate. In contrast, almost all of the patients with ulcers in the risedronate group, had these detected at both day eight and day 15.

These and other endoscopy trials have shown alendronate to be clinically well tolerated, with no clear association between endoscopy findings and upper GI tract adverse events evident. In these trials, endoscopic abnormalities were common at baseline, and it is suggested that most endoscopy findings are not clinically relevant.

Long-term trial data

Data emerging from large randomised controlled trials, involving approximately 19,000 participants for up to seven years, has not revealed a consistent or important difference between the tolerability and safety profiles of alendronate and placebo.

Upper GI tract adverse events are common among postmenopausal women, however data from three large phase 3 studies have not shown a significant difference in the rate of adverse GI events, in patients on placebo, alendronate irrespective of the dose (**Table 1 & 2**).

Table 1. Incidence of upper GI tract adverse events in alendronate phase 3 osteoporosis treatment studies*

		Alendronate		
Patients with upper GI tract AEs (%)	Placebo (n = 397)	5 mg/d (n = 202)	10 mg/d (n = 196)	20/5 mg/d† (n = 199)
Overall	39.0	36.6	42.3	40.2
Drug related‡	14.9	16.8	15.3	19.1
Serious	0.8	1.5	0.5	2.5
Resulting in withdrawal	2.0	3.5	1.0	2.0

*AEs = adverse events; GI = gastrointestinal.
†20-mg/d dose for the first 2 years and 5 mg/d during year 3.
‡Rated by the investigator as possibly, probably, or definitely drug related while blinded to treatment.

The most comprehensive investigation of the upper GI safety and tolerability of alendronate was conducted as part of the Fracture Intervention Trial (FIT). The study randomised women to placebo or alendronate (5 mg/day during the first 2 years and 10 mg/day thereafter) for up to 4.5 years. The number of alendronate and placebo patients who had reported at least one upper GI tract adverse event by the end of the first year was approximately 30%, a value that had increase to almost 50% by the end of the study. However, there was no significant difference between the two groups in terms of discontinuation of therapy or incidence of events, despite the large sample of patients and the large number of upper GI tract events reported. The incidence of upper GI tract events considered worrisome (oesophageal and gastroduodenal PUBs) or serious (requiring hospitalisation, considered life-threatening or disabling) was also not significantly different between the two groups.

Table 2. Incidence of upper GI tract adverse events in large trials of alendronate (ALN) in postmenopausal women*

Attribute	FIT† (3-4.5 y)[9]		FOSIT‡ (1 y)[45]	
	Placebo No. of patients (%)	ALN (5/10 mg/d) No. of patients (%)	Placebo No. of patients (%)	ALN (10 mg/d) No. of patients (%)
No. enrolled	3223	3236	958	950
Completed study	3042 (94)	3038 (94)	865 (90)	832 (88)
Upper GI tract AE	1490 (46.2)	1536 (47.5)	185 (19.3)	202 (21.3)
Abdominal pain	422 (13.1)	443 (13.7)	81 (8.5)	95 (10.0)
Dyspepsia	617 (19.1)	588 (18.2)	22 (2.3)	24 (2.5)
Oesophagitis	14 (0.4)	24 (0.7)	5 (0.5)	4 (0.4)
Oesophageal ulcer	7 (0.2)	6 (0.2)	NR	NR
Gastritis	75 (2.3)	82 (2.5)	20 (2.1)	26 (2.8)
Gastric ulcer	27 (0.8)	26 (0.8)	1 (0.1)	4 (0.4)
Duodenitis	4 (0.1)	7 (0.2)	NR	NR
Duodenal ulcer	11 (0.3)	4 (0.1)	3 (0.3)	0 (0.0)
Acid regurgitation/reflux	269 (8.3)	279 (8.6)	24 (2.5)	22 (2.3)
Hospital admission due to upper GI tract AE	59 (1.8)	65 (2.0)	NR	NR

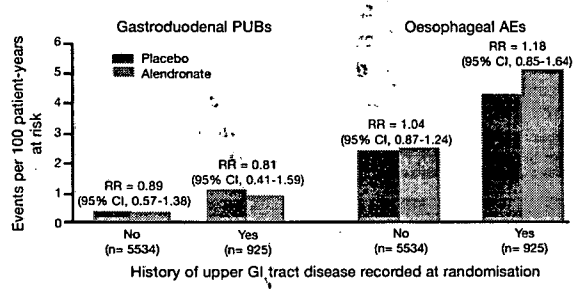
*No differences were significant ($P > 0.05$); significance levels were not provided for VERT –North America study. AEs = adverse events; EPIC = Early Postmenopausal Intervention Cohort; FIT = Fracture Intervention Trial; FOSIT = Fosamax International Trial; GI = gastrointestinal; NR = not reported; VERT = risedronate vertebral fracture studies.
†Age 55 to 80 years, bone density T score ≤–1.6,with or without vertebral fracture; major upper GI tract disease (eg,ulcer in past year or twice in past 5 years,upper GI tract bleeding within past 5 years,daily dyspepsia medication); only 1.4%of screened women were excluded for these reasons.
‡Age <85 years, spine bone density T score ≤–2; major GI disease (eg,peptic ulcer or malabsorption) in past year or drug to inhibit acid secretion for > 2 weeks in past 3 months.

GI events in patients at risk

The investigators involved in the FIT study analysed the incidence of upper GI tract adverse events in patients seen to be at high risk, randomised to placebo or alen-

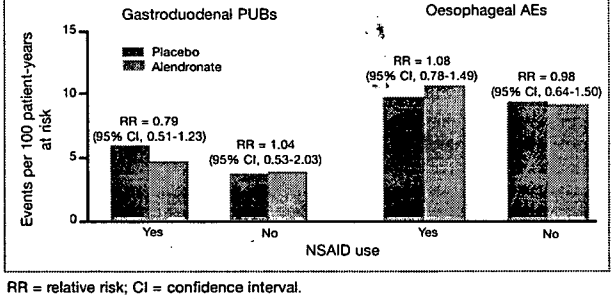
dronate. There was no significant difference in the rates of upper GI adverse events between patients classified as being at high risk due to age, NSAID use (**Figure 1**), or a history of GI tract disease (**Figure 2**), who were randomised to placebo or alendronate. In the FIT study, 88% of participants reported using NSAIDs during the course of the study, while 54% of participants reported a history of digestive system disorder that did not exclude them from enrolment.

Figure 1. Rate of oesophageal adverse events (AEs) and gastroduodenal perforations, ulcerations, and bleeding (PUBs) among alendronate- and placebo-treated women by history of upper gastrointestinal (GI) tract disease at baseline.



RR = relative risk; CI = confidence interval.

Figure 2. Rate of oesophageal adverse events (AEs) and gastroduodenal perforations, ulcerations, and bleeding (PUBs) among alendronate- and placebo-treated women according to nonsteroidal anti-inflammatory drug (NSAID) use at the time of the event.



RR = relative risk; CI = confidence interval.

In two six-month trials that randomised patients to alendronate (40 mg/day), the dosage employed in patients with Paget's disease, alendronate was well tolerated, with adverse event profiles similar to patients on placebo or etidronate (400 mg/day).

Comparison of dosing schedules

Some in vivo studies carried out in animal models have pointed to a possible increase in GI tract irritation in cases where dosing is frequent (daily), where there is repeated exposure to both acidic conditions and bisphosphonates. Randomised controlled trials have been undertaken to compare the efficacy and safety of daily and weekly dosing regimens of alendronate. The once weekly dosing regimen of alendronate 70 mg, has been shown to be therapeutically equivalent to daily dosing with alendronate 10 mg, while weekly dosing is also thought to encourage compliance.

A study by Schnitzer *et al* randomised 370 postmenopausal women with osteoporosis to receive alendronate 10 mg/day, 519 women to receive alendronate 70 mg once weekly and 369 women to receive alendronate 35 mg twice per week. Upper GI tract adverse events of any type were reported by 23.5%, 23.8% and 22.4% of the weekly, twice-weekly and daily dosing regimens respectively. No serious upper GI tract adverse events were reported in weekly or twice-weekly groups, while there was an incidence of 1.4% in the daily group. There was also a trend toward lower incidence of oesophageal, gastric and duodenal irritation for the weekly and twice weekly groups relative to the daily dosing group. The results from this and other studies show that weekly alendronate 70 mg, has a safety and tolerability profile similar to placebo in patients with osteoporosis and periodontal disease, similarly several studies also show that the incidence of upper GI tract adverse events for daily dosing with alendronate 10 mg is comparable to placebo.

Considerations

The results from large randomised controlled trials suggest that few patients report upper GI tract symptoms that are bothersome enough to warrant the discontinuation of alendronate. On the whole, evidence from large good quality randomised controlled trials does not support an association between alendronate and upper GI tract problems at doses used in clinical practice, when dosing instructions are heeded. Indeed, the low or absence of increased risk for GI tract adverse events is also found in patients perceived to be at increased risk of GI intolerance due to history of GI events (Figure 1) or current NSAID use (Figure 2).

So do the benefits or alendronate therapy out-way the risks? Considering the prevalence of osteoporosis, which is estimated at almost 2 million Australians, coupled with alendronate's demonstrated ability to decrease the incidence of spinal fractures (relative risk 0.52, 95% CI 0.43-0.65 [alendronate 5 – 40 mg]) and non-spinal fractures (relative risk 0.51, 95% CI 0.38-0.69 [alendronate 10 – 40 mg]) in osteoporotic patients, alendronate would certainly be regarded as providing benefit to many patients. In contrast, as indicated in this article, the incidence of oesophageal or other upper GI tract adverse events, has not been consistently seen in randomised trials, and appears to be close to or equal to that with placebo. Overall, risk benefit would certainly appear to support alendronate.

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Late-onset spondyloarthropathy mimicking reflex sympathetic dystrophy syndrome

J J Dubost, M Soubrier, J M Ristori *et al*
Joint Bone Spine (2003); **70**: 226–229

Spondyloarthropathy often presents with atypical symptoms in older patients, raising diagnostic problems. The subtle joint manifestations contrast with the severe constitu-tional symptoms and inflammation test disturbances, sug-gesting a malignancy, vasculitis, or infection. Nearly 40% of the patients have asymmetric edema in the lower limbs, which prompts a search for deep vein thrombosis or a pelvic space-occupying lesion[1].

We recently managed two patients in whom marked pain-ful edema in a lower limb with severe demineralization of the foot led experienced rheumatologists to give a diagnosis of reflex sympathetic dystrophy syndrome (RSDS). Laboratory tests showed inflammation, for which another explanation was sought. Both the patients were subsequently found to have late-onset peripheral spondyloarthropathy (LOPS)[2].

1. Case-report 1

A 62-year-old farmer experienced spontaneous onset of painful swelling of his right foot in December 1999. In May 2000, radiographs showed severe demineralization of the ankle and entire foot. The erythrocyte sedimentation rate (ESR) was 57 mm/h and the C-reactive protein (CRP) level was 82 mg/l. Naproxen therapy provided only short-lived relief. In July 2000, a Tc99m bone scan revealed marked diffuse hyperactivity of the ankle and foot, starting at the early vascular phase (**Figure 1**). RSDS was considered the most likely diagnosis. Salmon calcitonin therapy for 3 weeks was ineffective. In October 2000, ultrasonography and computed tomography (CT) showed marked thickening of the periar-ticular and sub-cutaneous soft tissues and diffuse demineral-ization, without joint lesions (Figure 1). The ESR was 83 mm/h and the CRP level was 100 mg/l. A rheumatologist diagnosed RSDS, prescribed griseofulvin therapy, and recommended evaluation of the inflammatory syndrome by an internist, who recommended hospital admission with investigations for a malignancy and a biopsy of the soft tissues and bone at the foot. Concern that the biopsy might exacerbate the RSDS prompted the rheumatologist to refer the patient to our de partment, in February 2001. Marked edema of the right foot and ankle was noted. Pitting was minimal. There were no vasomotor disorders. Other findings consisted of pain in the acromioclavicular joint and lateral acromion on both sides, as well as a small effusion in the right knee. His medical history was unremarkable, with only a 3-month-long episode of low back pain at 33 years of age. The ESR was 73 mm/h and the CRP level was 87 mg/l. The tests were negative for rheumatoid factors, antikeratin antibodies, antineutrophil cytoplasmic antibody, and antinuclear antibody. The HLA phe-notype was A2 B44 B27 DR1 DR13. Joint fluid from the right knee contained 18 100 cells/mm 3 with 73% of neutro-phils. Radiographic findings included severe demineraliza-tion of the right ankle, tarsal bones, and forefoot without joint space loss or effusions; bilateral sacroiliitis, and a syndesmo-phyte bridging L1 to L2 on the right. Radiographs of the knees were normal. A diagnosis of LOPS was given. Naproxen 550 mg bid was rapidly effective. Six weeks later, the edema had cleared, but arthritis was noted in the left tarsal joints. The ESR was 57 mm/h and the CRP level was 55 mg/l. The outcome was favorable with further non-steroidal anti-inflammatory drug (NSAID) therapy.

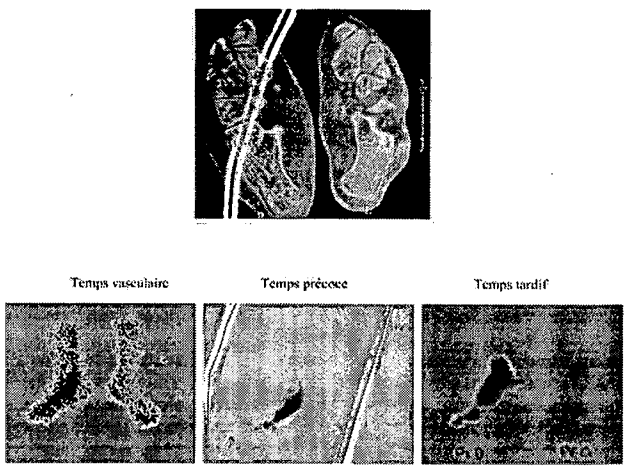

Fig. 1. Case 1. CT: diffuse demineralization of the right foot, normal joint spaces, and soft tissue thickening. Bone scan: marked diffuse hyperactivity of the foot and ankle at all three phases, from the early vascular phase to the late bone phase.

2. Case-report 2

Painful swelling of the right ankle and foot developed in May 2000, in this 75-year-old man, after a moderate-energy trauma. Radiographs taken in August 2000 showed severe patchy demineralization of the tarsal bones, forefoot, and ankle, without joint space loss (**Figure 2**). This pattern sug-gested RSDS. However, the results from the laboratory tests showing marked inflammation (ESR, 74 mm/h and CRP 78 mg/l) prompted admission of the patient. A low-grade fever of 37.8 °C was noted. He had no history of rheumatic disease. Joint fluid from the right ankle contained 3200 cells/mm³. Tests for rheumatoid factors were negative. The HLA pheno-type

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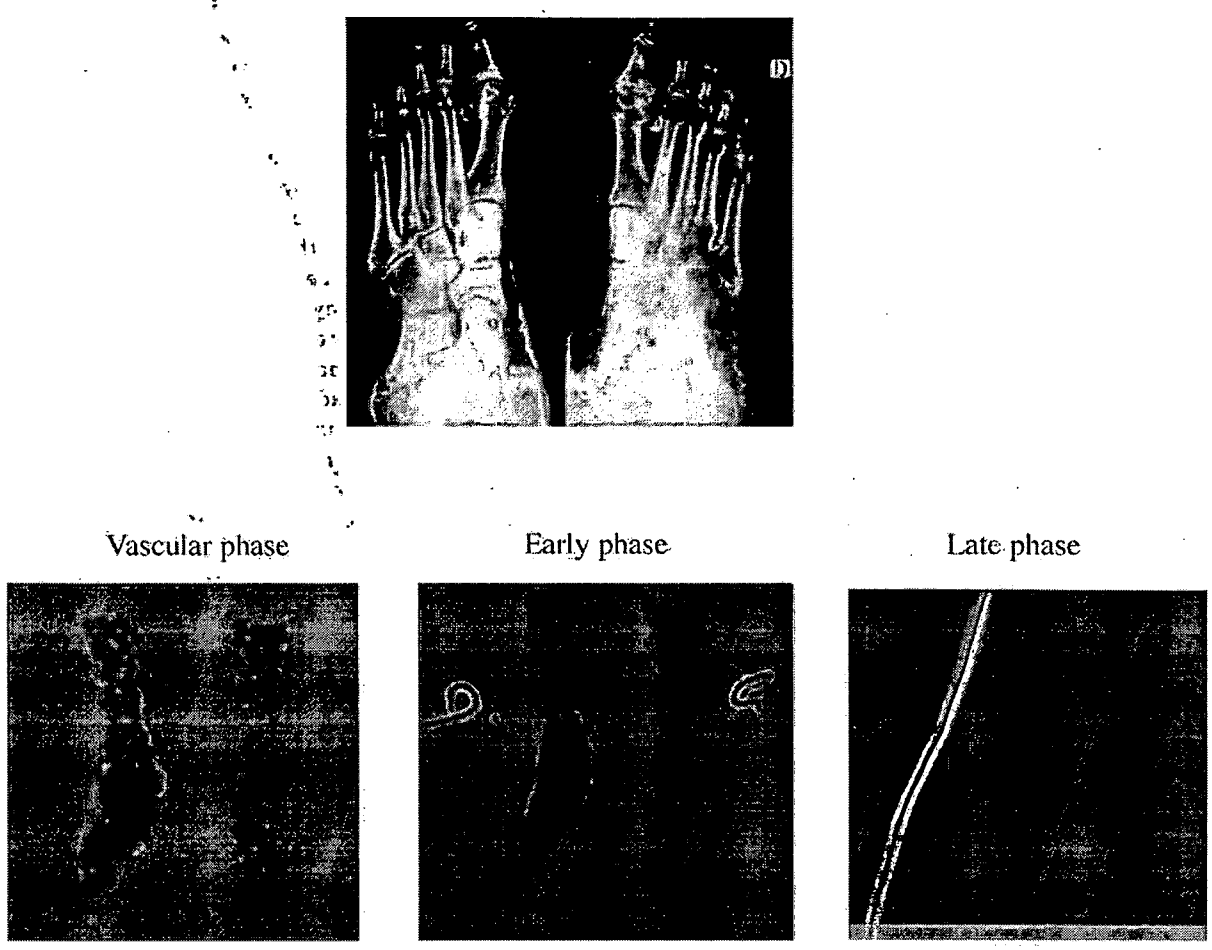

Fig. 2. Case 2. Plain radiographs: severe diffuse demineralization of the entire right foot with soft tissue thickening. Bone scan: marked diffuse hyperactivity of the foot and ankle at all three phases, from the early vascular phase to the late bone phase.

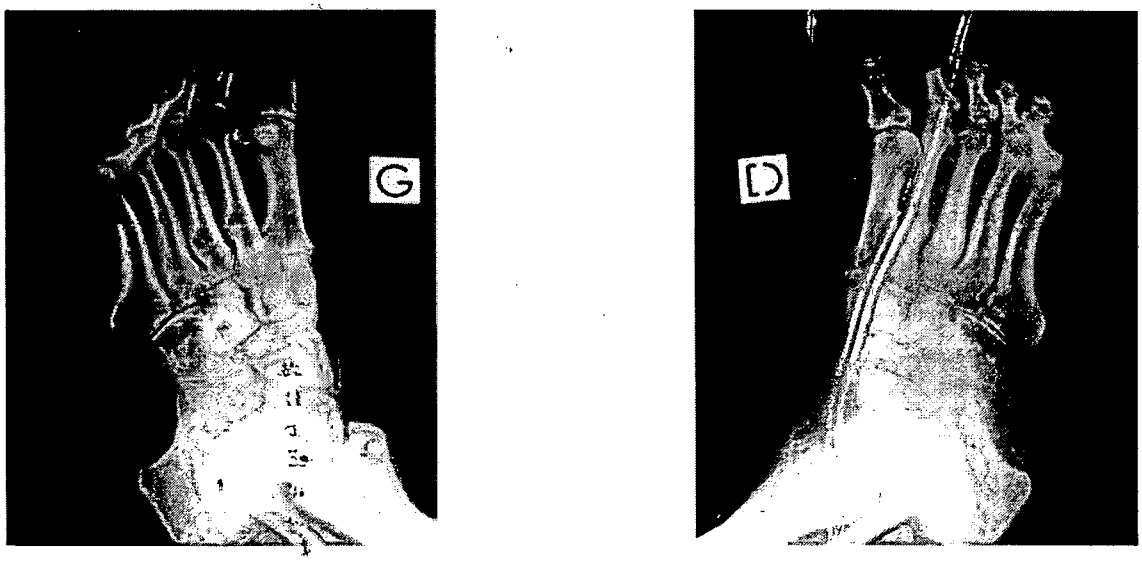

Fig. 3. Case 3. Radiographs: severe heterogeneous demineralization of the entire right foot.

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was A3 B18 B27 DR7 DR11. A Tc99m bone scan disclosed marked hyperactivity starting at the early vascular phase and involving the ankle, tarsal bones, and first metatarsophalangeal joint of the right foot (Figure 2), as well as the right knee and right sacroiliac joint. Magnetic resonance imaging showed effusions in the tibiotarsal and subtalar joints with normal bone signal. No significant abnormalities were seen on radiographs of the sacroiliac joints, and radio-graphs of the knees disclosed subchondral demineralization. No evidence of malignancy was seen on an ultrasound scan of the abdomen or a CT scan of the chest and abdomen. Indomethacin 100 mg/d improved both the clinical manifes-tations and the evidence of inflammation (CRP 17 mg/l). Three months later, he experienced a recurrence of the pain with marked pitting edema of the foot. Triamcinolone hexacetonide synovectomy of the ankle was ineffective. RSDS was considered again, and the patient was admitted for pamidr-onate therapy followed by rehabilitation therapy and hydro-therapy. In April 2001, arthritis developed in the right knee and left ankle. CRP was 43 mg/l. Fluid from the knee con-tained 7900 cells/mm 3 with no microcrystals. Radiographs of the right foot disclosed severe patchydemineralization without joint lesions. On radiographs of the right knee, sub-chondral demineralization was seen, but the joint space was normal. A diagnosis of LOPS was given. The treatment consisted in ketoprofen 300 mg/d and sulfasalazine 2 g/d. Three months later, he was free of pain and his ESR and CRP values were normal.

3. Discussion

In these two patients, the diagnosis of spondyloarthropathy was based on the presence of rheumatoid-factor negative asymmetric oligoarthritis of the lower limbs with a relapsing course, presence of HLA B27, and sacroiliitis visible on radiographs in one patient and by bone scanning in the other. In both patients, NSAIDs were only partly effective, as is often the case in the elderly[3]. The laboratory test evidence of severe inflammation, decline in general health, and asym-metric lower limb edema suggested other diagnoses, particu-larly cancer, although these features are also characteristic of LOPS[1]. At presentation, the edema with marked bony demineral-ization of the foot and ankle, the diffuse increase in radionu-clide uptake visible at the early vascular phase, and the precipitating trauma in case 2 led experienced rheumatologists to make a diagnosis of RSDS and to prescribe medica-tions appropriate for that condition (calcitonin, griseofulvin, pamidronate). The occurrence of RSDS in combination with inflammatory joint disease has been reported [4–7], and no argument rules out RSDS. However, in both patients, RSDS considered highly unlikely based on the following argu-ments: there were no trophic or vasomotor disorders, MRI in case 2 showed no bone signal abnormalities (although the investigation was done using an old machine), joint fluid was inflammatory (case 2), NSAID therapy was rapidly effective (case 1), and treatments for RSDS were ineffective. Immobilization-induced osteoporosis is not a convincing ex-planation to the severe demineralization because neither patient had a prolonged period without weight bearing; further-more, in both patients bone scanning showed marked diffuse hyperactivity.

In a retrospective study[1], another patient with LOPS had similar features. A 70-year-old man was admitted for marked painful edema of the right hand and subsequently of the right foot, with a decline in general health, low-grade fever, and ESR elevation (100 mm/h). Radiographs showed severe patchy demineralization (**Figure 3**) and bone scanning major diffuse hyperactivity. The tests were negative for rheu-matoid factors. He carried the HLA B27 antigen and had sacroiliitis on the right. The outcome was favorable under NSAID therapy. However, the demineralization persisted, prompting calcitonin therapy. In all three patients, the dem-ineralization may have been a consequence of the inflamma-tory process. The demineralization associated with inflam-matory joint disease is not usually as intense or diffuse. Thus severe diffuse demineralization, together with marked edema, may be suggestive of LOPS. Age-related changes in the inflammatory response to cytokines may attenuate the target organ response and facilitate diffusion to neighboring structures.

In practice, in an older patient, asymmetric lower limb edema with severe diffuse demineralization and the laboratory evidence of inflammation should suggest LOPS. Even in patients who report no other symptoms, a careful search for involvement of other joints is in order. The knee is of particu-lar interest because examination of a joint fluid sample can confirm the inflammatory nature of the joint disease.

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Therapeutic decisions in patients with arthritic pain, CV risk and /or GI sensitivity

Sub title

An on-going challenge for physicians is the treatment of patients with concomitant conditions or disease risk, and providing them with a combination of therapies that are effective and safe. Such situations often occur with patients who present with chronic pain such as arises with osteoarthritis, who may also have an increased risk of cardiovascular disease and/or gastrointestinal complications.

There is a need to clarify the medication strategies in these patients so that therapeutic efficacy can be maximized while minimizing risks. Data has been emerging to suggest that nonsteroidal anti-inflammatory drugs (NSAIDs) may interfere with the anti-platelet effects of aspirin.[1] While other data suggest a possible interference of aspirin with the gastrointestinal (GI)-sparing effect of cyclooxygenase-2 (COX-2) selective inhibitors (coxibs),[2] and there is other evidence showing that coxibs may exert cardiovascular effects.[3]

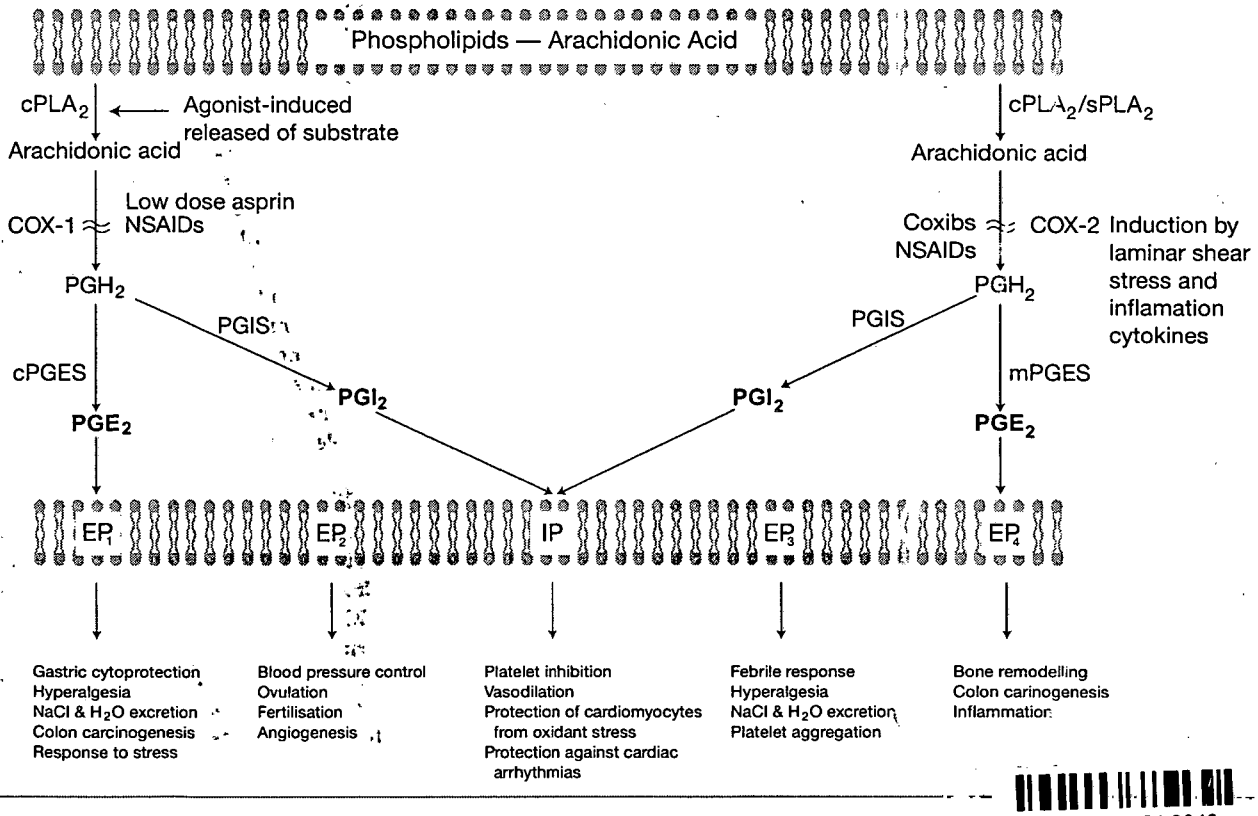
COX inhibitors – activities and side effects

The therapeutic analgesic, anti-inflammatory and anti-pyretic activities of conventional non-selective NSAIDs have been long recognised, as has their propensity to increase risks of side effects such as gastric and duodenal perforations and bleeding.[4] The increased understanding of the mechanisms of these drugs has had two important therapeutic outcomes. It has:

1. led to the recognition of the therapeutic beneficial anti-platelet activity of aspirin. It is now indicated for use in patients with known cardiovascular (CV) or cerebrovascular disease or as prophylaxis against acute myocardial infarction (MI), unstable angina, transient ischaemic attack and cerebrovascular accidents (stroke);[5]
2. led to the development of a new class of NSAIDs, coxibs, that have a reduced risk of GI side effects compared to non-selective NSAIDs.[4] Coxibs such as rofecoxib, were developed to maintain the analgesic and anti-inflammatory properties of NSAIDs, through blocking the COX-2 or prostaglandin H synthase type 2 (PGHS-2) enzyme, while having a better side effect profile, due to minimal interaction with the constitutively expressed COX-1 or PGHS-1 enzyme.

Since patients presenting to their physician often require low-dose aspirin for CV disease prophylaxis or treatment, as well as a non-selective NSAID or coxib for pain and inflammation, it is important to understand the various

Figure 1. Lipid bilayer showing the production and action of prostaglandin E_2 (PGE_2) and prostacyclin (PGI_2)



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factors that underlie the mechanisms of action of the three drugs, in order to make the correct therapeutic choices. The various therapeutic and side effect profiles of the NSAIDs, aspirin and coxibs are largely dependent on both the relative inhibitory activity on the two COX enzymes, ie selectivity, and the reversibility of the interaction between the drug and the enzyme.

Coxibs and cardiovascular disease

Several large randomised trials have demonstrated the lower risk of serious GI damage associated with the use of coxibs compared to that associated with non-selective NSAIDs.[2,3] The Vioxx Gastrointestinal Outcomes Research (VIGOR) study,[3] involving approximately 8000 patients with rheumatoid arthritis (RA) [rofecoxib is not indicated for the treatment of rheumatoid arthritis in Australia10], showed that patients allocated to rofecoxib (50 mg) [the maximum recommended daily dose in Australia is 25 mg10] experienced a higher risk of vascular events compared to patients on naproxen (500 mg twice daily) [the maximum recommended dose for RA in Australia is 1000 mg11]. Most of the difference between the two groups arose from incidence of MI, where patients in the rofecoxib group experienced 20 events in 2699 person-years of follow-up, compared with four events in 2699 person-years of follow-up among patients on naproxen; relative risk 0.20, 95% confidence interval [CI] 0.07-0.58.3 There was no significant difference in the incidence of stroke or vascular deaths between the two groups.3,7 The interesting question for physicians and their patients is whether the apparent increase in MI for patients on rofecoxib relative to naproxen is due to an increase for patients on rofecoxib, or a decrease on naproxen, or both?[3]

Dose naproxen have a cardioprotective effect?

No randomised trials have assessed the effect of naproxen on vascular events,[7] however in vitro studies have shown that in doses of 500 mg bid, it produces a > 90% inhibition of the vasoconstrictor platelet TxA_2 production throughout its dosing interval suggesting a beneficial effect on anti-platelet activity.[12,13] Some other NSAIDs such as indobufen and flurbiprofen have demonstrated a protective anti-platelet effect to a similar degree to low-dose aspirin,[14,15] and furthermore, it has been suggested that naproxen may also have a similar, though probably lesser, anti-platelet effect. The anti-platelet activity of aspirin has been shown to reduce the risk of MI by approximately one-third in patients, so if naproxen's anti-platelet effect were similar, it may be expected to also decrease MI similarly.

Does rofecoxib increase thrombosis?

Prostacyclin (PGI2) is a platelet anti-aggregant and vasodilator that works by antagonising the actions of TxA_2.[16] Naproxen has been shown to inhibit the synthesis of both PGI2 and TxA_2, while rofecoxib has minimal effect on TxA_2, but inhibiting the synthesis of COX-2-dependent PGI2. It has been suggested that arterial thrombosis in VIGOR may have been caused by rofecoxib, because it led to an accumulation of unopposed TxA_2 at the platelet-vascular endothelial interface, favouring

Mechanistic Considerations

Selectivity

The biochemical selectivity of the NSAIDs, aspirin and coxibs can be characterized using assays of products such as thromboxane B2 (TxB2) and prostaglandin E2 (PGE2).6,7 The selectivity is typically expressed as a ratio of the inhibitory concentration resulting in a 50% reduction (IC50) in COX-1 activity to the IC50 for COX-2 inhibition, as derived from in vitro studies (**Table 1**). These values only give an approximate estimate of the COX-1 inhibitory nature of a particular medication, due to considerable variability in plasma levels following dosing as well as other factors.

Table 1. Biochemical selectivity of current available COX-2 inhibitors, as measured in vitro with human whole-blood assays of COX-isozyme activity*

Inhibitor	COX-1:COX-2 IC_{50} ratio
Ibuprofen	0.5
Naproxen	0.7
Paracetamol	1.6
Indomethacin	1.9
Meloxicam	18.0
Nimesulide	19.0
Diclofenac	29.0
Celecoxib	30.0
Rofecoxib	267.0

* The 50% inhibitory concentration (IC_{50}) values for the inhibition of platelet cyclooxygenase 1 (COX-1) and monocyte COX-2 were obtained as described previously (4).

Reversibility and affinity

The structural interactions and kinetic parameters involved with the binding of NSAIDs, aspirin and coxibs with the COX enzymes has been studied with a view to determining the affinity and reversibility of these interaction. Low-dose aspirin (≤ 100 mg daily) has been found to irreversibly inhibit platelet COX-1 activity, resulting in a > 95% inhibition of thromboxane A2 (TxA_2) production and inhibition of TxA_2-mediated platelet aggregation throughout the 24-hour dosing interval.[7,8] Once COX-1 has been acetylated by aspirin, access to the catalytic site of the enzyme is blocked for the lifetime of the platelet.[7,8]

Aspirin also inhibits COX-1 in the gastric and duodenal mucosa resulting in a reduction of the PGE2-mediated cytoprotection against the acid milieu.[7,8] Most interactions of coxibs and NSAIDs other than aspirin, with the catalytic site of the COX enzymes are of a lower affinity compared with aspirin. The result of this is that the inhibition of the enzyme is more reversible, in some cases, however the dissociation of the drug molecule from the enzyme site, may still leave the enzyme inactivated.[9]

occlusive thrombus formation. However, this has been dispelled to some extent by the findings that coxibs only partially inhibit COX-2-derived PGI2, while leaving COX-1-derived PGI2 intact (**figure 1**),[7] meaning that TxA_2 is not completely unopposed in this regard. Furthermore there are other pathways not reliant on COX-2-derived PGI2, that facilitate thromboresistance, such as those involving nitric oxide.[7] Therefore the alteration of the ratio of endothelial prostacyclin to platelet-derived thromboxane by rofecoxib is thought to cause minimal increased risk for thrombosis.

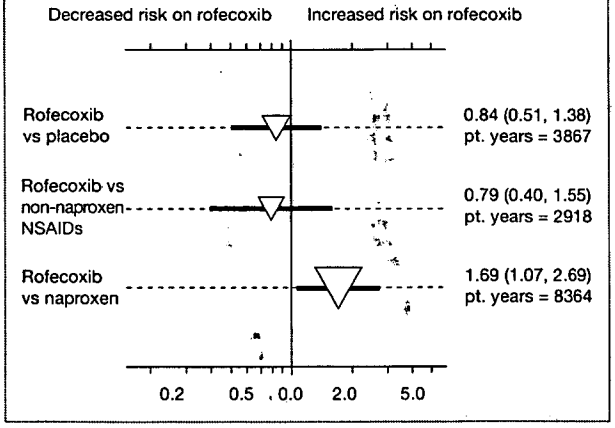
Is the increased MI risk to due to increased blood pressure effects?

Observational studies in apparently healthy individuals indicate that a prolonged increase in systolic BP of 10 mmHg is associated with a 25% higher risk of MI.7 Nonselective NSAIDs and coxibs are both known to induce an increase in BP through their effects on renal prostaglandins, although the relative difference in this effect between the two classes is not known. In the VIGOR study,[3] rofecoxib was associated with an increase in SBP of 3.6 mmHg compared to naproxen over one year, which, extrapolating from the epidemiological study,[3,7] would suggest an increase of 8% in MI risk for the coxib group, which is less than the reported -30% in VIGOR.[3,7]

Questions and hypotheses

A meta-analysis of data from more the 28,000 patients in randomised trial of rofecoxib by Konstam *et al*[17] found that rofecoxib was not associated with an increased risk of vascular events compared with placebo or non-naproxen NSAIDs (**Figure 2**). The authors of the meta-analysis suggest that the absence of an excess risk with rofecoxib, relative to placebo, argues against blood pressure elevation as an important factor in the differential effect compared with naproxen. Konstam *et al*[17] demonstrated a lack of association of rofecoxib with excess CV thrombotic events compared with placebo or non-naproxen NSAIDs, and they suggest (although do not supply evidence) that naproxen may provide a cardioprotective benefit.[17]

Figure 2. Relative risk (95% CI) of the APTC end point for rofecoxib relative to placebo, non-naproxen NSAIDs, and naproxen in the entire population studied. triangles represents relative risk, and size of triangles represents patient-years of exposure. Bars indicate 95% CI



The Celecoxib Long-term Arthritis Safety Study (CLASS) trial,[2] a similar study to VIGOR, of approximately 8000 patients with rheumatoid arthritis randomised to celecoxib (400 mg bid), ibuprofen (800 mg tid) or diclofenac (75 mg bid), failed to show an association of celecoxib with increased risk of serious cardiovascular thromboembolic events.

In summing up their conclusions of the reason for the increase in thromboembolic events in the VIGOR study with rofecoxib, Baigent *et al*[7] suggest "a combination of some cardioprotective effect of naproxen and chance does seem to offer a plausible explanation for these unexpected findings"...with ..."little evidence in humans to support a prothrombotic effect of coxibs."[7]

Interactions between aspirin and anti-inflammatory drugs

Careful consideration of drug combinations needs to be made in patients who present with arthritis or other inflammatory disorders, who are also at intermediate or high risk for vascular events. In these situations it is important to choose an appropriate anti-inflammatory to use in conjunction with aspirin. Two particular concerns have been identified:[7]

1. NSAIDs may interfere with the anti-platelet effect of aspirin
2. Aspirin may interfere with the GI-sparing effect of coxibs.

NSAIDs' interference with aspirin-effect

Some NSAIDs such as naproxen are thought to have reversible and short-term anti-platelet activity, while low-dose aspirin reliably produces irreversible inhibition of COX-1 enzymes resulting in complete and persistent inhibition of TxA_2-mediated platelet aggregation.[7] Since most NSAIDs do not have a predictable and prolonged effect of platelet aggregation,[7] it would not be prudent to rely on these drugs for cardiovascular prophylaxis, and instead administering low-dose aspirin is preferred, including cases where other NSAIDs are used to treat pain or inflammation. However, it has been observed that some NSAIDs antagonise the anti-platelet effects of aspirin, possibly through competitive binding to the active site of the COX-1 enzyme. In contrast, no such competitive binding has been observed with the COX-2 selective NSAIDs such as rofecoxib. Therefore, coxibs may be preferable to a conventional NSAID for patients requiring CV prophylaxis with aspirin (**Table 2**).[7]

Aspirin and the GI-sparing effect of coxibs

The GI-sparing ability of rofecoxib was clearly shown in the VIGOR study where a 50% lower incidence of serious GI complications was recorded compared to naproxen.[3] Celecoxib also resulted in reduced incidence of GI complications in the CLASS study compared to non-selective NSAIDs (ibuprofen or diclofenac), although this did not reach statistical significance.[2,7] In view of the excess risk of GI complications resulting from aspirin treatment, it has been suggested that patients treated with low-dose aspirin may derive substantial benefit from taking a coxib (due to their reduced risk of GI-complications), rather than a conventional NSAID.[18]

Flawed analysis of data from the CLASS trial suggested that celecoxib was only superior to an NSAID in patients who were not taking aspirin regularly for prevention of cardiovascular disease.[7] Problems with the statistical analysis and interpretation of these data mean that the evidence arising from the study is not clear about whether the GI-sparing effects of celecoxib and the conventional NSAIDs differed according to aspirin co-administration.[7]

Risks of CV disease in patients on NSAIDs or coxibs

The choice of NSAID or coxib may be contingent on whether or not aspirin is to be co-administered. The annual absolute risk for vascular events should be determined in a patient before making the judgment about whether low dose aspirin is appropriate for CV prophylaxis for patients on anti-inflammatory agents.

Data suggest that for patients with:

- o > 3% per year risk of a vascular event, aspirin should be considered;
- o 1–3% per year risk of a vascular event, aspirin should be considered in selected patients;
- o < 1% per year risk, the balance of benefit and risk of aspirin are far from clear.

A meta-analysis19 of published data from trials of aspirin versus placebo among low risk individuals suggested that the estimated vascular event rate should exceed 0.8% per year before the benefit of aspirin could be assumed to exceed the risks of bleeding. The findings presented here appear to confirm the benefit of individualised patient treatment and in particular, the selection of patients for aspirin treatment requires consideration of risk factors for cardiovascular disease including gender and age, and also the presence of comorbid conditions such as rheumatoid arthritis, diabetes or gastrointestinal senstivity.

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Practice points

- There appears to be no evidence for a GI benefit for conventional NSAIDs over coxibs in aspirin-treated patients. Therefore, in patients at intermediate or high risk of GI complications, it would seem appropriate to consider coxibs irrespective of the concomitant use of aspirin **(Table 2)**.
- The decision to administer aspirin should be made based on the annual risk of vascular events.
- In patients with low risk of GI complications, the choice of anti-inflammatory drug should depend on whether aspirin is to be co-administered.
- Conventional NSAIDs may interfere with the anti-thrombotic efficacy of aspirin, therefore coxibs are a rational choice if aspirin is to be prescribed.
- In cases where no aspirin is required then either conventional NSAIDs or coxibs are can be made.
- In order to minimize GI toxicity, the lowest effective dose of conventional NSAID or coxib should be carefully evaluated in the individual patient.
- When co-prescribing a coxib and aspirin, the lowest effective dose of aspirin should be used.

Table 2. Suggested strategy for analgesic/antiinflammatory treatment and cardiovascular prevention among patients with inflammatory disease and different levels of risk of vascular events and gastrointestional (GI) complications*

Risk of vascular event† \ Risk of serious upper GI complications	Low (<0.2% per year)	Intermediate (0.2–0.5% per year)	High (>0.5% per year)
Low (<1% per year)	NSAID or coxib, no ASA	Coxib, no ASA	Coxib, no ASA
Intermediate (1-3% per year)	NSAID or coxib if ASA indicated‡	Coxib ± low-dose ASA	Coxib ± low-dose ASA
High (>3% per year)	Coxib + low-dose ASA ‡	Coxib + low-dose ASA	Coxib + low-dose ASA§

* Based on observational studies (47), the absolute risk of a serious upper GI complication (defined as upper GI bleeding, perforation, or other GI-tract event resulting in death, hospitalisation, or visit to specialist) among nonusers of nonsteroidal antiinflammatory drugs (NSAIDs) is <0.02% per year among individuals age <50 years, but increases to >0.5% per year among elderly individuals age ≥80 years. The absolute excess risk of serious upper GI complications associated with NSAID use may be (conservatively) estimated ~3 times the baseline risk, and the use of a highly selective coxib may reduce this excess risk by ~50%. ASA = aspirin.

† Vascular event is defined as the combined outcome of a nonfatal myocardial infarction, nonfatal stroke, or vascular death (6 .

‡ For patients at low baseline risk of GI complications and requiring aspirin, a coxib may be preferable to avoid the potential for loss of antiplatelet efficacy when an NSAID is prescribed with aspirin (36). For patients at low risk of GI complications and not requiring aspirin, the absolute benefit of using a coxib in lieu of a traditional NSAID may be too small to justify any additional cost.

§ For patients at high risk of vascular events in whom the presence of risk factors for serious upper GI complications (e.g., older age, previous history, or steriod use) implies a particularly high risk of such complications, pharmacologic cytoprotection might be considered appropriate.

Alendronate and risedronate: What you need to know about their upper gastrointestinal tract toxicity

DE Baker
Reviews in Gastroenterological Disorders 2002; **2**: 20-33

Adverse upper gastrointestinal (GI) tract events can occur with alendronate or risedronate therapy. Although short-term, non-placebo-controlled comparisons of alendronate and risedronate indicated that risedronate therapy may be associated with a lower risk of upper GI toxicity than alendronate therapy, the placebo-controlled comparison shows no difference in the risk of upper GI toxicity between the two drugs. The risk of an adverse upper GI event increases when these drugs are used concurrently with nonsteroidal anti-inflammatory drug (NSAID) therapy, but this incidence is no more than that observed with concurrent placebo and NSAID therapy. Also, the risk of these adverse GI tract events can be decreased by following the dosing instructions (eg, avoid lying down for 30 minutes after taking the drug and take the drug with a full glass of water) and may be decreased with once-weekly dosing.

Gastrointestinal tolerability of the selective cyclooxygenase-2 (COX-2) inhibitor rofecoxib compared with nonselective COX-1 and COX-2 inhibitors in osteoarthritis

DJ Watson, SE Harper, P-L Zhao *et al*
Archives of Internal Medicine 2000; **160**: 2998-3003

Background
Most nonsteroidal anti-inflammatory drugs (NSAIDs) are nonselective cyclooxygenase (COX-1 and COX-2) inhibitors and are associated with a variety of upper gastrointestinal (GI) tract symptoms. The roles of COX-1 and COX-2 in the pathogenesis of these symptoms are unclear. To test whether COX-2 inhibition with rofecoxib would have greater GI tolerability than nonselective COX-1 and COX-2 inhibition, we compared the incidences of (1) treatment discontinuations for GI adverse events (AEs) and (2) prespecified dyspeptic-type GI AEs among patients with osteoarthritis treated with rofecoxib vs NSAIDs.

Methods
A prespecified, combined analysis of investigator-reported GI AEs in all eight double-blind, randomized, phase 2b/3 osteoarthritis trials of rofecoxib was conducted. Patients included men and women with osteoarthritis (n = 5435); there was no upper age limit for entry. Treatments tested included rofecoxib, 12.5, 25, or 50 mg (combined), vs ibuprofen, diclofenac, or nabumetone (combined). Primary outcomes were the time (by survival analysis) to (1) treatment discontinuation due to GI AEs and (2) first reported dyspeptic-type GI AE. Between-treatment comparisons were made by log-rank test.

Results
The number of treatment discontinuations caused by GI AEs during 12 months was significantly lower (p = 0.02) with rofecoxib vs NSAIDs (8.2 vs 12.0 per 100 patient-years; relative risk (RR), 0.70; 95% confidence interval (CI), 0.52–0.94). The incidence of prespecified dyspeptic-type GI AEs during the first six months was significantly lower (p = 0.02) with rofecoxib vs NSAIDs (69.3 vs 85.2 per 100 patient-years; RR, 0.85; 95% CI, 0.74–0.97). However, the difference between treatments in dyspeptic-type GI AEs was attenuated after six months.

Conclusion
Rofecoxib was associated with a lower incidence of treatment discontinuations due to GI AEs over 12 months and a lower incidence of dyspeptic-type GI AEs over six months than treatment with nonselective COX inhibitors, or NSAIDs.

Upper gastrointestinal tolerability of celecoxib compared with diclofenac in the treatment of osteoarthritis and rheumatoid arthritis

F McKenna, L Arguelles, T Burke *et al*
Clinical and Experimental Rheumatology 2002; **20**: 35-43

Objective
To compare the upper gastrointestinal (UGI) tolerability of celecoxib (a cyclooxygenase-2 specific inhibitor) and diclofenac using data from three randomised, double-blind clinical trials in osteoarthritis (OA) and rheumatoid arthritis (RA).

Methods
Patients in two OA studies received either celecoxib 100 mg BID (n = 545), diclofenac 50 mg BID or TID (n = 540), or placebo (n = 200) for six weeks. In the RA study, patients received celecoxib 200 mg BID (n = 326) or diclofenac 75 mg BID (n = 329) for 24 weeks. The cumulative incidence of abdominal pain, dyspepsia, nausea or any of these events (UGI tolerability composite endpoint) after the first 6 weeks was estimated using time-to-event analysis.

Results
In the pooled OA trials, the cumulative incidence of the composite endpoint was significantly higher with diclofenac (17.6%; 95% CI: 14.4–20.9%) than celecoxib (11.1%; 95% CI: 8.4–13.8%; p = 0.002) and comparable with placebo (13.3%; 95% CI: 8.1–18.4%; p = 0.157). In the RA trial, the cumulative incidence of the UGI tolerability composite endpoint was also significantly higher with diclofenac (20.7%; 95% CI: 16.3–25.1%) than celecoxib (15.9%; 95% CI: 11.9–20.0%; p = 0.013). Celecoxib

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was also better tolerated than diclofenac in this trial in terms of the cumulative incidences of abdominal pain ($p = 0.031$) and dyspepsia ($p = 0.062$). The results of the UGI tolerability composite endpoint analysis were confirmed using the Cox proportional hazards model to control for other predictors of UGI adverse events.

Conclusion
The UGI tolerability of therapeutic dosages of celecoxib was significantly better than diclofenac in patients with RA or OA.

A comprehensive review of treatments for postmenopausal osteoporosis

HJ Häuselmann and R Rizzoli
Osteoporosis International 2003; 14: 2-12

Background
The aim of this review is to assess the efficacy of treatments for postmenopausal osteoporosis in women with low bone mass or with an existing vertebral fracture.

Method
We searched the literature for studies (randomized, double-masked, placebo-controlled and prospective) that reported on drugs registered in Europe or North America. We included 41 reports on 12 agents. To assess the consistency among the studies for each drug, we plotted the percent change in bone mineral density (BMD) for the control group against the percent change in BMD for the treated group for lumbar spine and femoral neck. We used methods of cluster analysis to determine consistency among the studies. For each agent we summarized the relative risk for vertebral fracture (patients with new fracture) and for hip fractures. The duration of the studies ranged from 1 to 4.3 years.

Results
The proportion of patients who discontinued treatment ranged from 4% to 80%. Most of the studies reported data on change in BMD. Twenty-six studies (10 drugs) provided data on new vertebral fractures and 12 (6 drugs) on hip fractures. Apart from fluoride effects on spine BMD, increases in BMD with bisphosphonates were greater than those seen with the remaining treatments. Generally, for each agent the changes in BMD (relative to placebo) were consistent among the studies. The exceptions were calcitriol and calcitonin for changes in BMD of the spine and of the femoral neck. Alendronate, calcitonin, risedronate and raloxifene caused significant reductions in the risk of vertebral fractures. Alendronate, risedronate or the combination of calcium plus vitamin D had a significant effect on the risk of hip fracture.

Conclusion
Most therapies are effective in increasing BMD; some decrease the risk of vertebral fracture. For hip fracture, alendronate and risedronate reduce the risk in women with osteoporosis, and calcium and vitamin D reduce the risk in institutionalized patients.

New possibilities for diagnosis and treatment of osteoporosis

PD Miller
International Journal of Fertility and Women's Medicine 2001; 46: 215-221

Postmenopausal osteoporosis is preventable and treatable. Women need not lose bone mineral density (BMD) after the menopause. Without intervention, all women lose bone after menopause, regardless of the amount of calcium, vitamin D, and exercise they undertake. Postmenopausal women need estrogen replacement, a selective estrogen receptor modulator (SERM), or a bisphosphonate to prevent bone loss. Alendronate, risedronate (bisphosphonates) and raloxifene (SERM) are approved for the prevention of bone loss. The diagnosis of at-risk postmenopausal women can best be accomplished by measuring BMD in all postmenopausal women aged 65 years and older regardless of their risk profile and in all postmenopausal women under 65 years with one or more risk factors. Treatment guidelines direct physicians to treat postmenopausal women with T-scores lower than -2.0 SD regardless of their risk profile and postmenopausal women with T-scores lower than -1.5 SD with one or more risk factors. The lower the BMD, the greater the fracture risk, particularly in individuals with increased age, existing fragility fractures, or high bone turnover. The best intervention for a patient should be individually selected, based on careful clinical assessment. Although calcitonin is not approved for prevention, it is approved for treatment. The labeling of estrogens has been modified to state that they may be used to "manage" osteoporosis. The lack of efficacy of calcitonin to prevent bone loss during the first five years after menopause, and the lack of prospective fracture reduction data for estrogen, have resulted in these labeling restrictions. Alendronate, risedronate, and raloxifene are currently approved for the treatment of osteoporosis. These compounds have been shown to increase BMD and decrease fracture risk. The monitoring of a patient's response to treatment may be accomplished using serial BMD testing and biomarkers of bone turnover.

Long-term tolerability of the bisphosphonates in postmenopausal osteoporosis: A comparative review

RB Kherani, A Papaioannou and JD Adachi
Drug Safety 2002; 25:781-790

Background
Osteoporosis in postmenopausal women is a growing health concern for society. Bisphosphonates have become the mainstay of prevention and treatment with the mounting evidence of their efficacy over the past two decades. This review article examines the use of the etidronate, alendronate and risedronate.

Method
The pivotal trials are reviewed for long-term tolerability, evidence regarding histological safety and gastrointestinal tolerance. Etidronate, alendronate and risedronate have also been examined in meta-analyses, which reviewed methodologically sound trials. Length of treatment, adverse events and medication discontinuation and patients lost to follow-up were evaluated.

Results
Etidronate trials and the recent meta-analysis support the safe clinical use of cyclical etidronate with no signs of osteomalacia or other skeletal pathology over two to three years. In addition to increased bone mineral density (BMD) and vertebral fracture risk reduction, patients tolerated cyclical etidronate well up to four years in randomised studies. Non-randomised data has shown safety up to seven years with clinical and bone biopsy data. Alendronate studies demonstrated similar overall adverse event rates, study discontinuation rates and loss to follow-up rates between placebo and treatment arms, in addition to consistent improvements in BMD, vertebral and non-vertebral fracture risk reductions over three to four years. Histological safety has been demonstrated up to three years. Longer-term therapy in non-randomised trials up to seen years showed similar clinical safety between alendronate and placebo. Risedronate trials and the meta-analysis also showed similar adverse event profiles between placebo and treatment arms, as well as improvements in BMD, vertebral and non-vertebral fracture risk reductions up to three years. Rates of discontinuation due to gastrointestinal events were similar between groups. Histological safety has also been demonstrated for risedronate up to three years.

Conclusions
Each of these bisphosphonates has been shown to have comparable safety with placebo up to three to four years, with the most rigourous trials carried out for alendronate and risedronate. Long-term comparative studies are awaited.

Gastrointestinal safety of coxibs and outcomes studies: What's the verdict?

L Laine
Journal of Pain and Symptom Management 2002; **23**(Suppl 1): S5-S10

Background
Although nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used, their main limitation is gastrointestinal (GI) injury. Two double-blind, randomized, outcomes trials were conducted to determine the incidence of clinical GI events with the coxibs, rofecoxib and celecoxib, compared with nonselective NSAIDs. The VIGOR study (VIOXX Gastrointestinal Outcomes Research) compared rofecoxib with naproxen, and the CLASS study (Celecoxib Long-term Arthritis Safety Study) compared celecoxib with ibuprofen and diclofenac.

Results
The VIGOR trial revealed a relative risk reduction for clinical upper GI events of 50% with rofecoxib, and a 60% reduction in complicated events. In the CLASS study, the 23% reduction in complicated ulcers with celecoxib did not reach statistical significance (p = 0.45), although when all clinical events were examined, the 34% reduction was significant (p = 0.04). However, low-dose aspirin use, which was allowed in the CLASS study, may have influenced the results. A subgroup analysis in the patients who did not take aspirin revealed a nonsignificant 45% reduction in complicated events with celecoxib (p = 0.19), and a 47% reduction in complicated and symptomatic ulcers (p = 0.02).

An endoscopic comparison of the effects of alendronate and risedronate on upper gastrointestinal mucosae

F Lanza, H Schwartz, B Sahba *et al*
American Journal of Gastroenterology 2000; **95**: 3112-3117

Objectives
The nitrogen-containing bisphosphonates alendronate and risedronate have been reported to have upper gastrointestinal (GI) safety and tolerability profiles comparable to those of placebo. Nevertheless, both agents have demonstrated similar potential for irritation of gastric mucosa at high doses in preclinical studies. The present study compared the potential for alendronate and risedronate to produce endoscopic upper GI mucosal irritation using the highest approved dosage for the two agents.

Methods
This was a multicenter, randomized, parallel-group, double-blind, placebo-controlled trial in which a total of 235 patients (men or postmenopausal women, aged 45–80 years) with normal upper GI endoscopy at baseline received 28-day treatments with the following: alendronate 40 mg/day (n = 90), risedronate 30 mg/day (n = 89), placebo (n = 36), or placebo with aspirin 650 mg q.i.d. for the last seven days (n = 20). Endoscopy was repeated on day 29 using standardized scoring scales.

Results
After 28 days of treatment, the alendronate and risedronate groups had comparable mean gastric and duodenal erosion scores that were significantly lower than those of the aspirin group. Esophageal scores were comparable in all groups. Gastric ulcers and/or large numbers of gastric erosions occurred in approximately 3% of alendronate and risedronate patients versus 60% with aspirin. Both bisphosphonates were clinically well tolerated.

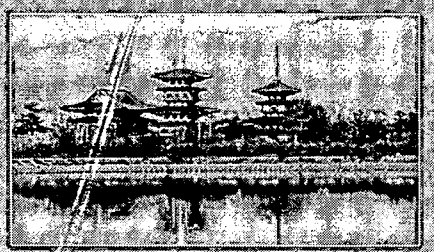
Conclusions
The potential for gastroduodenal irritation is similar for alendronate and risedronate and is markedly less than for aspirin. The findings of this study, together with the large placebo-controlled clinical trial experience with both agents and extensive epidemiological data for alendronate, suggest that the risk for clinically important gastric irritation with these bisphosphonates is very low, even at the highest available doses.

Conference highlights

EULAR 2003

European Congress of Rheumatology

Lisbon, Portugal,
18–21 June, 2003



IBMS 2003

1st Joint Meeting of the International Bone and Mineral Society
and the Japan Bone and Mineral Society

Osaka, Japan,
3–7 June 2003

Rofecoxib evaluated in real-time conditions

Citation

Evaluation of rofecoxib under real-life conditions in Mexico – Analysis of satisfaction with treatment and patients' quality of life

R Espinosa-Morales, E Hunsche, J Querol et al

Background

Numerous clinical trials of osteoarthritis (OA) have demonstrated rofecoxib to be as effective as traditional nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). This study analysed the impact of treatment with rofecoxib on patients' quality of life and also evaluated satisfaction of patients and physicians with the treatment.

Methods

A pre-post comparative, open-label, short-term, observational study was conducted in which 76 physicians from three large Mexican cities participated between 5 August and 22 November 2002. Each physician enrolled up to 12 patients with OA of the hand, hip, or knee, who had been taking NSAIDs for pain relief prior to enrollment (baseline). Patients discontinued NSAID therapy and continued on rofecoxib 25 mg once daily for the following two weeks, after which a follow-up visit was scheduled. Patients and physician questionnaires were administered at baseline as well as the follow-up visits to collect data on demographics, disease history, drug treatment patterns, patients' quality of life, and treatment satisfaction. Paired sample t-test was used to detect differences in patients' responses between baseline and follow-up.

Results

The preliminary results from 425 patients are presented here. The mean age of the patients was 58.3 years, and 72% of them were women, with a mean BMI 28.0 kg/m^2. 46.1% of the patients were full- or part-time workers. Hypertension (30%), obesity (31%) and back pain (26%) were the most common comorbidities. At baseline, 32% of patients reported dyspepsia, 49% reported gastritis, and 29% pyrosis. When compared to prior NSAID treatment, 49.8% of physicians were very satisfied with the analgesic and 50.8% were very satisfied with the anti-inflammatory effects of rofecoxib; 35.1% and 38.4% indicated being satisfied, the others reported being slightly satisfied, slightly dissatisfied, dissatisfied, or very dissatisfied. From the patients questionnaires, 35.1% and 38.4% answered that they were much more satisfied (based on a six-point Likert scale) with the pain relief and the amount of pain relief, respectively, provided by rofecoxib compared to the pain medications they took before; 47.4% and 45.8% of patients reported being more satisfied.

The quality of life of patients improved under rofecoxib the average improvement in SF-8 scores was statistically significant for all 8 domains: 14.9 (general health), 11.3 (physical functioning), 12.1 (role physical), 14.9 (bodily pain), 11.0 (vitality), 11.0 (social functioning), 10.7 (mental health), and 9.2 (role emotional) (all $p < 0.0001$). After the 14 days of treatment with rofecoxib, the Patient Global Assessment of Disease Status (PGADS) improved by 43.7 points (0-100 scale) from baseline to follow-up ($p < 0.0001$).

Conclusion

Treatment of osteoarthritis using rofecoxib provides significant improvements in quality of life and pain relief compared to comparative NSAIDs, as reported by patients and physicians in this open-label trial.

Rofecoxib in hip and knee OA patients

Citation

Rofecoxib improves quality of life in hip and knee OA patients

R Theiler, D Uebelhart, H Bischoff et al

Aim

This trial aimed to determine whether patients with pain flares due to knee or hip osteoarthritis (OA), which are not sufficiently responsive to conventional nonsteroidal anti-inflammatory drugs (NSAIDs), will experience an improvement in their quality of life through treatment using rofecoxib 25 mg/day. Secondary aims were to quantify the percentage of patients who required concomitant gastroprotective medication such as proton pump inhibitors during the drug treatment period and also to measure the effects of NSAID treatment. One other objective was to validate the use of a new electronic version of the WOMAC 3.1LK in a multisite setting.

Methods

One hundred and thirty-four elderly patients with a mean age of 69.1 ± 8 years were enrolled in the trial. The participants, who had symptomatic hip or knee osteoarthritis, were screened and those who fulfilled the criteria were switched from conventional NSAID therapy to rofecoxib 25 mg daily for three weeks. Patients were instructed to monitor and record their consumption of other analgesic rescue medication such as paracetamol, as well as their use of gastroprotective medication. A clinical examination and self-assessment were performed by filling out the SF-12 and the WOMAC 3.1 LK questionnaire at each control visit (day 7, 14, 21). Ten of the 20 study sites used the electronic WOMAC version. A telephone survey was undertaken two weeks after the end of the rofecoxib therapy to record the ongoing drug consumption.

Results

Quality of life measured by the SF-12 physical function score significantly improved. The relative treatment effect after 3 weeks was an improvement of 29% for pain, 25% for stiffness and 24% for function. At the end of the study 54% of patients continued the drug therapy with rofecoxib, whereas 31% switched back to another drug (mostly diclofenac). Only 8% of the patients needed co-medication to relieve adverse GI-symptoms. There was good agreement between the paper and computer format of the e-WOMAC and all users were able to use the computerised questionnaire quite well.

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Conclusion
Rofecoxib improved quality of life of hip and knee OA patients, who were not sufficiently responsive to conventional NSAID therapy in this three-week study. Furthermore, the e-WOMAC appears to be a suitable tool to assess OA patients in clinical trials.

CV safety of rofecoxib in the elderly with comorbidities

Citation
Cardiovascular safety profile of rofecoxib in elderly patients with Alzheimer's Disease or cognitive impairment: an updated pooled analysis
A Reicin, P DiBattiste, S Mukhopadhyay et al

Background
An updated analysis of pooled safety data from rofecoxib clinical trials in elderly patients was performed to investigate the cardiovascular (CV) safety of this selective COX-2 inhibitor.

Methods
Adverse event data were examined from two completed studies in patients with Alzheimer's disease and one ongoing study in patients with Mild Cognitive Impairment (interim data). The data from these three randomised, double-blind, placebo-controlled studies of rofecoxib 25 mg were pooled. The analysis included serious thrombotic CV adverse events. Two data sets were examined: (1) confirmed serious thrombotic CV events blindly adjudicated by an external committee according to a pre-defined standard operating procedure; (2) confirmed events meeting the criteria of the Antiplatelet Trialists' Collaboration (APTC). Event rates per 100 patient-years and relative risks with 95% confidence intervals (CI) were calculated for each dataset. The analysis included data available as of 31 January 2002 and updates previous reports.

Results
The analysis included data from a total of 1453 patients who received rofecoxib 25 mg, and 1454 patients who received placebo. The median age of patients was 76 years in the rofecoxib group and 75 years in the placebo group. The mean duration of treatment was 1.2 years in the rofecoxib group and 1.3 years in the placebo group. The results of the analysis are shown in the accompanying table. A relative risk < 1 indicates reduced risk for rofecoxib versus placebo.

Table 1. Number of cases/patient-years at risk (rate per 100 patient-years at risk)

Serious CV adverse events	Rofecoxib 25 mg n = 1453	Placebo n =1454	Relative risk [95% CI]
Confirmed-adjudicated	37/1699 (2.18)	48/1925 (2.49)	0.86 [0.56, 1.33]
APTC	30/1705 (1.76)	41/1934 (2.12)	0.82 [0.51,1.32]

Conclusion
This group of elderly patients who would generally be considered to be at increased risk for CV events experienced relatively few serious cardiovascular adverse events during the course of their trials, with rofecoxib showing a similar CV safety profile to placebo.

Selective prescribing of a COX-2 inhibitor

Citation
Selective prescribing of COX-2 inhibitors: Results of a French survey on rofecoxib prescriptions
BG Bannwarth, I Logeart, G Vergult

Background
Cyclooxygenase (COX)-2 selective inhibitors are more expensive on a day-to-day basis than conventional nonsteroidal anti-inflammatory drugs (NSAIDs). On the other hand, the use of coxibs has been reported to be cost-effective in patients at high risk of gastrointestinal (GI) events with NSAIDs. Thus it is important to examine whether coxibs are preferentially prescribed for high-risk patients.

Objectives and Methods
To assess the prescribing patterns of rofecoxib versus conventional NSAIDs in clinical practice in France. A representative sample of 1010 French general practitioners recorded the demographic, medical and pharmaceutical characteristics of all patients for whom they prescribed an NSAID between 1 July, 2001 and 30 June, 2002.

Results
The prescribing patterns of rofecoxib were similar for both available dosages (12.5 and 25 mg). About 75% of the patients were dispensed rofecoxib for the treatment of osteoarthritis while off-label prescribing was less than 15%. The mean age of patients receiving rofecoxib (59.5 years) was significantly higher than that of patients receiving a conventional NSAID (44.8 years). A history of peptic ulcer or GI bleeding was recorded in 4.8% of the patients in the rofecoxib group vs 2.1% in the standard NSAID group. Low dose aspirin and antihypertensive medications were being taken in 6.1% and 34.8% of the patients, respectively, in the rofecoxib group versus 2.3% and 15.6%, respectively, in the conventional NSAID group. Concurrent use of a proton pump inhibitor was marginally less frequent in the rofecoxib group (16.9%) compared with the standard NSAID group (18.6%). However, a significantly higher proportion of patients were given a proton pump inhibitor prior to rofecoxib therapy (10.4%) than prior to conventional NSAID therapy (3.7%).

Conclusion
Our findings suggest that French GPs are more likely to prescribe rofecoxib than a conventional NSAID for patients who have comorbidities and/or risk factors associated with NSAID gastropathy.

Bisphosphonates plus HRT in elderly women

Citation

Effects of alendronate and hormone replacement therapy, alone or in combination, on bone mass and markers of bone turnover in elderly women with osteoporosis

S Eviö, A Tiitinen K Laitinen et al

Aim

To compare alendronate, hormone replacement therapy (HRT), and their combination in treatment of elderly postmenopausal women with osteoporosis.

Methods

Ninety patients, aged 65-80 (mean 71) years, and with a T-score of bone mineral density (BMD) < 2.5 at either the lumbar spine or the femoral neck were randomised to receive 10 mg of alendronate (n = 30), 2 mg of estradiol plus 1 mg norethisterone acetate (n = 30) (HRT), or their combination (n = 30) for two years. BMD of the lumbar spine and the upper femur was measured at baseline and after one and two years of treatment. Urinary excretion of type I collagen aminoterminal telopeptide as related to creatinine (U-NTX) and serum type I procollagen aminoterminal propeptide (S-PINP) were assayed at baseline and at six-month intervals thereafter.

Results

Increases of 9.1–11.2 % in lumbar spine BMD at two years were similar in the study groups. Only HRT increased femoral neck BMD statistically significantly ($p < 0.0001$) at both one (+4.9%) and two years (+5.8%; $p < 0.05$ for differences to the other groups). The alendronate group exhibited the biggest increases in trochanter BMD both at one (+5.8%; $p < 0.01$ for differences to the other groups) and two years (+8.5%; $p < 0.01$ for a difference to the combination treatment group). Total hip BMD increased similarly in all study groups. Percent reductions in U-NTX in the HRT group (60.2–62.7%) were significantly less ($p < 0.05$) than in the combination group (78.1–80.4%) and in the alendronate only group (72.4–76.1%). Also S-PINP decreased less ($p < 0.05$) in the HRT group (-53.6% to -59.8%) than in the other groups (-73.0% to -75.0% in the alendronate group; -67.0% to -71.5% in the combination group). Six patients discontinued the study due to gastrointestinal complaints (two in each group), and five receiving HRT due to breast tenderness.

Conclusion

We conclude that in elderly postmenopausal women with osteoporosis the combination of hormone replacement therapy and alendronate did not offer an extra gain of bone mass over either treatment alone. In terms of BMD changes the single treatments were equally effective, but the reductions in bone markers were less on HRT than on alendronate.

Head-to-head comparison of alendronate and risedronate

Citation

Once weekly alendronate produces a greater increase in bone mineral density than daily risedronate

D Hosking, S Adami, D Felsenberg et al

Background

We report the 12-month Bone Mineral Density (BMD) results of the first head-to-head trial designed to compare the efficacy of alendronate and risedronate for the treatment of osteoporosis.

Methods

The 3-month, randomized, double-blind, multicenter international study with double-blind extensions for an additional nine months (12 months in total), enrolled 549 postmenopausal women.

Patients were 60–90 years old (mean, 69), with osteoporosis defined by low BMD T-score (either lumbar spine or total hip/femoral neck less than/equal -2.5, or less than/equal -2.0 at both sites). Patients maintained a calcium intake of at least 1000 mg daily through food and/or calcium supplements.

Patients were randomized into three treatment groups: alendronate 70 mg once weekly using standard am dosing; risedronate 5 mg daily dosed 2 hours after a meal and at least 2 hr before the next; or matching placebo for each. The results are based on a modified intention-to-treat approach of lumbar spine and hip BMD at month 12.

Table 1. Percent change from baseline month 12 at lumbar spine, femoral neck, trochanter, and total hip.

BMD site					
		LS mean			
Treatment	N	Lumbar spine	Femoral neck	Trochanter	Total hip
Placebo	99-101	0.1	-0.1 1.5† 2.2†	-0.7 0.8* 3.2†	-0.2 0.9† 2.7†
RIS 5 mg daily	206	2.8†			
ALN 70 mg OW	188-190	4.8†			
Between-treatment comparison					
		LS mean difference			
Treatment		Lumbar spine	Femoral neck	Trochanter	Total hip
ALN 70 mg - PBO		4.7†	2.4†	3.9†	2.8†
RIS 5 mg daily - PBO		2.7†	1.6†	1.5*	1.1¶
ALN 70 mg OW - RIS 5 mg daily		2.0†	0.8*	2.4†	1.7†

† $p < 0.001$; ¶ $p < 0.01$; * p 0.05; between-groups and within-group test of LS (least-squares) mean percent change.
ALN: Alendronate; PBO: Placebo; RIS; Risedronate; OW; Once-weekly.

Results and discussion
In this study, alendronate 70 mg once weekly produced significantly greater BMD increases over 12 months than did risedronate 5 mg daily, at the spine and all hip sites. These differences may be due to the superior anti-resorptive efficacy of alendronate 70 mg once weekly, reduced bioavailability of risedronate resulting from post-meal dosing, or both.

Long-term efficacy of alendronate

Citation
Ten-year efficacy and safety of alendronate in the treatment of osteoporosis in postmenopausal women
RD Emkey, I Reid, AL Mulloy et al

Background
Alendronate sodium (ALN) inhibited bone resorption, reduced the risk of vertebral fractures and progressively increased BMD over three years in a study of 994 osteoporotic women. We now report the results for 247 women who entered a final three years extension (years 8–10).

Results
During years 6 to 10, patients in the ALN 5 and 10 mg groups remained on the same doses. Patients in the ALN 20/5/placebo (A-PBO) group (20 mg for two years, 5 mg for three years) received placebo in years 6 to 10. Significant increases in spine BMD of 2.25 % with ALN 10 mg and 1.60 % with 5 mg were found during years 8 to 10, and prior increases in hip and total body BMD were maintained.

Forearm BMD was stable with 10 mg but decreased slightly with 5 mg. Women in the A-PBO group who had not been treated with ALN since the end of year 5 showed no significant change in spine and total body BMD, but small decreases in hip and forearm BMD occurred during years 8 to 10. Cumulative 10 year spine BMD increases were 13.7 % with ALN 10 mg and 9.8 % with 5 mg.

The safety and tolerability profiles of ALN 5 and 10 mg were similar to placebo during both years 8 to 10 and years 6 to 10. The three-year incidences of non-vertebral fractures during years 8 to 10 were 8.1, 11.5, and 12.0 % in the ALN 10 mg, 5 mg and A-PBO groups.

The three year incidences in the original cohort during years 1 to 3 were 8.5 % (pooled ALN) and 10.7 % (placebo). Neither stress fractures nor fracture malunion were reported.

Conclusion
We conclude that ALN treatment is effective for 10 years and is generally well tolerated. Spinal BMD continues to increase over 10 yrs and other skeletal benefits are maintained. Non-vertebral fracture data indicate similar risk over time, and suggest that fracture risk reduction is maintained during continued treatment. Discontinuation of ALN after five years leads to bone loss at non-spine sites, and continued treatment with ALN through 10 years yields sustained skeletal benefits.

Bone turnover at 6 months

Citation
Efficacy of Fosamax vs. Evista comparison trial (effect-international): Resulys at 6 months
P Sambrook, P Geusens, V Keraudren et al

Background
This multinational study was designed to compare the efficacy of alendronate and raloxifene when used for treatment of osteoporosis in postmenopausal women. We presented here the six month results from this 12 month study.

Methods
This study population comprised 487 postmenopausal women at 50 centers in 15 countries representative of Eastern and Western Europe, Asia-Pacific, and South America. Patients were randomly assigned in a 1:1 ratio to receive alendronate 70 mg once weekly (Fosamax, Merck & Co., Inc.) and raloxifene placebo daily or raloxifene 60 mg daily (Eli Lilly) and alendronate placebo once weekly.

This interim analysis assessed the response in markers of bone turnover at 6 months. The markers measured were urinary NTx and serum BSAP. The mean age of women enrolled was 62 years (range 42 to 90 years). Seventy-nine were Caucasian. They were, on average, 15 years post menopause.

Results
At six months, the decrease in urinary NTx from baseline in the alendronate group was 68.1%, compared to a decrease of 28.6% in the raloxifene group ($p < 0.001$). The decrease in serum BSAP from baseline in the alendronate group was 43.8%, compared to a decrease of 11.1% in the raloxifene group ($p < 0.001$).

For both urinary NTx and serum BSAP, changes from baseline within treatment group were significant for both treatments ($p < 0.001$ for both alendronate and raloxifene). This study is planned to continue through a 12 month treatment duration.

Conclusion
The six month results presented here indicate that weekly alendronate provides larger decreases in bone turnover than does daily raloxifene, and is therefore a more potent antiresorptive agent when used for treatment of osteoporosis in postmenopausal women.

Helping osteoarthritis patients return to normality can be very satisfying, but doing so can be a complex process, calling for a combination of approaches.

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VIOXX (rofecoxib, MSD)
A step in the right direction

1 Cannon GW et al Arth & Rheum 2000; 43(5): 978-987. 2 Langman MJ et al JAMA 1999; 282(20): 1929-1933. 3 Bombardier C et al N Engl J Med 2000; 343: 1520-1528. 4 Zacher J et al Curr Med Res Opin 2002; 18(4): 229-236. * ibuprofen, diclofenac and naproxen.

PBS Information: Restricted benefit. Symptomatic treatment of osteoarthritis.

Note: The use of rofecoxib for the treatment of the following conditions is not subsidised through the PBS: acute pain, soft tissue injury, arthrosis without an inflammatory component.

VIOXX® (rofecoxib, MSD) Use: COX-2 inhibitor; Osteoarthritis and Rheumatoid Arthritis. Contra: Active peptic ulcer; GI bleeding; asthma, urticaria or other reactions to NSAIDs incl aspirin; concomitant NSAIDs. Prec: History of peptic ulcer; GI bleeding; high dose, prolonged use; alcoholism; dehydration; asthma; oedema; hypertension; heart failure; infection (masks fever); hepatic, renal impairment; elderly, debilitation; pregnancy, lactation, children. Adverse: GI upset include perforation, ulceration, bleeding; anaphylactoid reactions (possible); hepatic and renal effects; anaemia; fluid retention; hypertension; confusion; rash; others, see full PI. Interact: Steroids, anticoagulants; smoking (incr risk of GI event); hepatic enzyme inducers e.g. rifampicin; theophylline; drugs metabolised by CYP1A2 e.g. amitriptyline, tacrine; ACE inhibitors; aspirin; lithium; diuretics (possible) Tablets: Fix Rofecoxib; lactose; cream (12.5 mg) yellow (25 mg) Packs (30). Dose: OA, 12.5 – 25 mg once daily; RA, 25 mg once daily Dispensing Price: 12.5 mg, $29.40; 25 mg, $42.79. Refer to full Product Information before prescribing. Product information is available directly from Merck Sharp & Dohme or by reviewing MIMS CD or MIMS Annual, 2003.

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