Drug Safety 1998 Aug; 19 (2): 141-154
0114-5916/98/0008-0141/$07.00/0

A Risk-Benefit Assessment of Alendronate in the Treatment of Involutional Osteoporosis

Jean-Pierre Devogelaer

Department of Rheumatology, Saint-Luc University Hospital, Louvain University in Brussels, Brussels, Belgium

Contents

Abstract

Osteoporosis is the most frequent metabolic condition experienced by elderly individuals. It is characterised by a low bone mass and microarchitectural deterioration of bone tissue leading to an increase in bone fragility and susceptibility to fracture. Osteoporosis constitutes a significant financial burden for health services as well as a source of pain and disability and a cause of a decrease in the quality of life for patients with the condition. Effective therapy for osteoporosis is, therefore, urgently needed. Currently, a number of different therapeutic approaches exist that have more or less proven positive effects on the incidence of fractures, for example estrogen replacement therapy, calcitonin, fluoride salts, calcium plus vitamin D supplementation and the first-generation bisphosphonate etidronate (etidronic acid).

Alendronate (alendronic acid) is an alkylaminobisphosphonate with a very potent antiresorptive capability. In contrast to etidronate, alendronate possesses an excellent ratio between its potency for inhibiting bone resorption and its po-

tency for impairing bone formation. In addition, no case of focal or generalised osteomalacia has so far been observed with alendronate. The bioavailability of oral alendronate is poor and the agent has to be taken in a fasting state, at least 30 minutes before breakfast, with a full glass of water.

Alendronate has demonstrated its ability to increase bone mass significantly above the placebo values at any studied skeletal site in a wide variety of patient subgroups regardless of age, race, baseline rate of bone turnover or baseline bone mineral density. Alendronate is the only medication with a demonstrated positive effect on symptomatic and asymptomatic vertebral fracture rate, as well as on nonvertebral fracture rate. In clinical trials, alendronate was generally well tolerated and no significant clinical or biological adverse experiences were observed. However, postmarketing data have included reports of oesophageal lesions compatible with the diagnosis of alendronate-induced chemical oesophagitis, in around 1% of patients taking the agent. However, in the vast majority of cases alendronate tablets had been taken incorrectly. Therefore, with proper use, that is, use complying with the manufacturers administration recommendations, this potentially dangerous complication should be minimised and should not outweigh the overall positive benefit of alendronate in the prevention of fractures.

1. Osteoporosis

Osteoporosis is the most frequent metabolic condition experienced by elderly individuals. It is a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture.[1] Osteoporosis constitutes a major public health problem, leading to a decrease in the quality of life, to disability and even to death through its major symptomatic manifestation, the fracture, particularly of the hip. In a study of 50 year old women from Rochester in the US, the life-time fracture risk was estimated to vary from 17.5%, [95% confidence intervals (CI) 16.8 to 18.2] at the proximal femur, to 15.6% (CI 14.8 to 16.3) for the vertebrae, to 16.0% (CI: 15.7 to 16.7) at the distal forearm and to 39.7% (CI: 38.7 to 40.6) for any of these fracture sites.[2] These figures fit very well with clinically observed fracture rates amongst 70-year-old Danish women, as far as postmenopausal osteoporotic fractures are concerned.[3] With such numbers in mind, there is no doubt that therapy aimed at preventing osteoporosis should be a major consideration, in order to curtail the financial burden for health systems and to alleviate the pain, disability and decreased quality of life experienced by patients with this condition. Different pharmacological approaches have been investigated for treating osteoporosis.[1]

2. Structure and Activity of Bisphosphonates

The bisphosphonates are stable analogues of the naturally occurring inorganic pyrophosphate which contains a cleavable core P-O-P structure. They are characterised by P-C-P bonds, where the presence of a carbon instead of an oxygen atom confers resistance to hydrolysis and to degradation by pyrophosphatases. The main biological effect of bisphosphonates is to inhibit bone resorption,[4] but they may also inhibit bone mineralisation. The ratio of their potency of inhibition of bone resorption to bone mineralisation varies from 1 bisphosphonate to the other. This ratio is notably less favourable for etidronate, the first of these compounds to be commercially available, which in clinical trials provoked osteomalacia that was focal in the vast majority of patients,[5] but generalised in a very few cases.[6] The clinical significance of these histomorphometric findings is unclear, because, overall, no clinically relevant consequence of overt osteomalacia has so far been reported. To date, no such

effects have been reported for alendronate (alendronic acid) either in animal models (beagle dogs),[7] or in humans.[8] Alendronate, like disodium pamidronate, belongs to the alkylaminobisphosphonate class,[9] with a basic primary nitrogen atom within the alkyl chain. This confers an increased antiresorptive potency,[10] but also potentially provokes adverse effects such as an acute phase-like reaction[11] and upper gastrointestinal adverse effects.[12]

The exact mechanism of action of bisphosphonates on osteoclast-mediated bone resorption is not yet fully understood. Proposed mechanisms include cytotoxic or metabolic injury to the mature osteoclast, inhibition of osteoclast attachment to bone surface, inhibition of osteoclast differentiation or recruitment and impairment of osteoclasts through the mediation of osteoblasts. Cytotoxicity for osteoclasts could involve individual cell necrosis or induction of apoptosis, a physiological form of programmed cell death. If excessive, this mechanism of action could theoretically end up in freezing bone remodelling, with the risk of compromising the mechanical resistance by a decreased capability for repairing microfractures. In animal studies involving minipigs, baboons and adult dogs, alendronate has been found to have no adverse effect on bone strength.[7,13-15]

3. Pharmacokinetics of Alendronate

The oral bioavailability of bisphosphonates is generally poor and, in particular, the oral bioavailability of alendronate, as determined from animal studies, is only l to 2%.[16] There is no metabolism of alendronate; the drug that reaches the systemic circulation is either distributed to bone, where it is sequestered for a long time – a potential source of long term complications in the case of allergy or hypersensitivity[17] – or excreted in the urine. In clinical trials with alendronate 10 mg/day, there has been no significant increase in reports of rashes as compared with placebo.[8]

In postmenopausal women, the mean oral bioavailability of alendronate 10mg was found to be 0.82% (90% CI 0.59 to 1.14) following overnight fasting and ingestion 2 hours before breakfast.[18] Eating immediately before ingestion of the alendronate or even 2 hours before administration, almost completely suppressed the absorption of the drug in many patients. Waiting 30 to 60 minutes after administration before eating produced an approximately 40% loss of bioavailability, with no significant difference between the 30 and 60 minute wait.[18] Supplementing meals with lg of elemental calcium did not affect the absorption of alendronate any more than the meal itself.[18] Both black coffee and plain orange juice reduced absorption by about 60% relative to administration with water.[18] It is therefore crucial to administer alendronate in a fasting state, at least 30 minutes before breakfast, with plain water. With improper administration, the risk of loss of activity of the drug is considerable. In contrast, oral bioavailability was approximately doubled by the increase in gastric pH produced by concomitant ranitidine and this could also occur in elderly people with hypochlorhydria or achlorhydria, potentially raising concern for safety.[18]

4. Efficacy of Alendronate in the Treatment of Osteoporosis

4.1 Effect on Bone Mass

A multicentre, placebo-controlled, double-blind, randomised trial of alendronate 5 or 10 mg/day for 2 years, 20 or 40 mg/day given for 1 year, followed by placebo for 1 year, produced a significant increase in the bone mineral density (BMD) of the lumbar spine of postmenopausal women.[19] In this study, the 10 mg/day dosage produced a significantly greater increase in BMD at the total hip than any other dosage. Moreover, the total hip BMD continued to increase significantly in the group receiving 10 mg/day in the second year of the study, whereas significant changes were not seen in the other groups.[19]

Since evidence has shown that alendronate 10 mg/day is more effective than 5 mg/day, this dosage, administered 30 to 60 minutes before breakfast for patient convenience and compliance, is the

dose approved by US Food and Drug Administration (FDA) for the treatment of postmenopausal osteoporosis. The effects of placebo, alendronate 5 and 10 mg/day on BMD obtained are summarised in table I.[19-23] In a 3 year study, Devogelaer et al.[21] found that over 92% of patients receiving alendronate 10 mg/day had an increase in spine BMD at year 3 compared with baseline.

In another study, Tucci et al.[22] found that 94.3% of patients taking alendronate 10 mg/day had an increase in lumbar spine BMD of ≥4% and none had a decrease, whereas 57.5% of the patients receiving placebo showed a loss of spine BMD. Of utmost importance was the fact that, in this study, the effects of alendronate in increasing BMD were similar in a wide variety of patient subgroups irrespective of age, race, baseline rate of bone turnover or baseline BMD.[21] In addition, alendronate completely prevented the loss of total body and forearm BMD that was seen in patients receiving placebo. This suggests that the increase in BMD observed both at the spine and at the hip were not acquired at the expense of bone mass elsewhere in the skeleton.[21]

The effects of alendronate on lumbar and hip BMD were maintained for up to 5 years in an extension of studies by Devogelaer et al.[21] and Tucci et al.[22] In this extension,[24] the percentage of patients with a positive lumbar BMD response (i.e. >0%) was 90.2, 97.2 and 94.3% for alendronate 5, 10 and 20 mg/day, respectively, administered for 2 years followed by 5 mg/day for 3 years. The gains in BMD seemed to level off, however, beyond the fourth year of therapy.[24]

4.2 Effect on Fractures

4.2.1 Vertebral Fractures

Only 2 studies to date have provided a reliable effect of alendronate on vertebral fracture rate.[25,26] Both of these studies lasted for 3 years. Studies lasting 2 years undertaken to date have not shown any clear-cut effect of alendronate on the number of vertebral fractures.[20,23] The frequently cited study of Liberman et al.[25] is in fact an analysis of pooled data from 2 studies differing in location but similar in protocol (1 was multinational[21] and the other was conducted in the US[22]). In these studies, postmenopausal osteoporosis was defined on the basis of a lumbar BMD meeting the WHO criteria for osteoporosis,[27] i.e. lower or equal to 2.5 standard deviation (SD) below the mean for young premenopausal women. Incidentally, with such a low BMD at the spine, some patients developed vertebral fractures, according to a definition based on a digitisation technique of lateral x-rays of the spine.[28] There was

Table I. Effect of placebo and alendronate on bone mineral density in various studies of postmenopausal osteoporosis[19-23]

Drug/duration	% Change from initial values					
	lumbar spine	femoral neck	femoral trochanter	total hip	1/3 distal forearm	total body
Placebo						
12mo	–0.7 to +0.3	–0.5	+0.7	NS	–0.2	–0.2
24mo	–1.4 to +0.6	–0.7 to –2.6	–0.3 to +0.2	–1.2	–0.5 to –2.0	–0.2
36mo	–0.6 to –0.8	–0.7 to –1.6	–0.4 to –0.9	–0.9	–1.7 to –2.0	–0.9 to –1.0
Alendronate 5 mg/day						
12mo	+3.8 to +5.5	+1.0	+3.3 to +3.5	NS	NS	+0.8
24mo	+5.1 to +7.3	+1.6 to +3.0	+4.1 to +5.1	+3.6	NS	+1.4 to +1.6
36mo	+4.9 to +5.6	+2.9	+4.7 to +5.1	+3.7	–0.4 to –0.6	+0.3 to +1.0
Alendronate 10 mg/day						
12mo	+3.9 to +5.8	+2.2	+4.4	+4.2	NS	NS
24mo	+5.2 to +7.8	+1.2 to +5.0	+6.0 to +6.8	+5.3	NS	+2.5
36mo	+6.8 to +9.6	+4.7 to +4.8	+6.9 to +7.4	+5.0	+0.3 to +0.6	+1.6

NS = not stated.

no assessment of clinical fractures and no estimation of the impact on the quality of life of the observed vertebral deformities.

After 3 years, 22 patients receiving placebo had developed at least 1 new vertebral fracture versus 17 patients in the combined alendronate groups. The risk of developing new vertebral fractures amounted to 6.2% in the placebo group versus 3.2% in the combined alendronate groups, with a relative risk of 0.52 (95% CI 0.28 to 0.95) in the alendronate combined groups versus placebo. The risk of developing 2 or more vertebral fractures (i.e. with supposedly a larger impact on the quality of life) was reduced from 4.2% in the placebo group to 0.6% in the combined alendronate groups. As already known,[29] the presence of previous vertebral fractures in this study also increased the risk of developing new vertebral fractures in both placebo and combined alendronate therapy groups (19.1% and 13.4%, respectively). This should be compared with the risk observed in patients without prevalent fractures (2.0 and 1.0%, respectively).

At similar levels of BMD of the lumbar spine, there was a trend for a differing fracture risk in the US population as compared to the multinational population both in the placebo and combined alendronate therapy groups (4.5% and 7.9%, respectively, in the placebo groups and 1.6 and 4.9%, respectively, in the treated groups), to the disadvantage of the multinational groups. Thus, fracture risk may differ in different populations notwithstanding similar BMDs.[30]

Table II. Patients with new vertebral fractures in the Fracture Intervention Trial (FIT) study (after from Black et al.,[26] with permission)

	Number of women with vertebral fractures (%)[a]		Relative risk (95% CI)
	placebo	alendronate	
Morphometric fractures			
≥1	145 (15.0)	78 (8.0)	0.53 (0.41-0.68)
≥2	47 (4.9)	5 (0.5)	0.10 (0.05-0.22)
≥4	13 (1.3)	0 (0.0)	
Clinical vertebral fractures	50 (5.0)	23 (2.3)	0.45 (0.27-0.72)

a Among 965 women in placebo groups, there were 240 morphometric fractures in 145 women. Among 981 women in alendronate groups, there was 86 morphometric fractures in 78 women.

CI = confidence interval.

The study by Black et al.,[26] one arm of the Fracture Intervention Trial (FIT) involving 2027 women with a previous vertebral fracture, was conducted to investigate the effect of alendronate on fracture rate. As such, it has been so far the only randomised, controlled trial to examine this relationship.[31] In this study, the distinction was also made between clinical and morphometric vertebral fractures. Postmenopausal women included in this trial had a BMD at the femoral neck about 2.1 SD below peak bone mass based on the densitometer manufacturer's normative data, and had experienced at least 1 prevalent (morphometrically defined) fracture. The initial alendronate dosage administered was 5 mg/day. However, according to data that became available once the trial was in progress, showing that a 10 mg/day dosage produced significantly greater increases in bone mass than 5 mg/day,[19-23] with similar tolerability, the dose in this trial was therefore blindly doubled for each participant at her 24-month follow-up visit. The double-blinding was maintained. The effect of alendronate on new vertebral fractures is summarised in table II.[26]

It is important to note that after 2 years of receiving alendronate 5 mg/day, 42 (4.4%) patients in the active therapy groups and 109 (11.6%) patients in the placebo group had experienced new vertebral fractures. Thus, alendronate 5 mg/day also seems to be effective as far as the prevention of vertebral fractures is concerned.

In the other arm of the FIT study,[32] 4432 postmenopausal women with low BMD, but without any pre-existing vertebral fracture, were randomised to receive either alendronate or placebo. Alendronate 5 mg/day for 2 years followed by 10 mg/day administered for mean of 2.25 years, reduced the risk of morphometrically-defined vertebral fractures by 51% (fracture rate 3.5% in placebo recipients versus 1.7% in alendronate recipients; relative risk 0.49, 95% CI 0.32 to 0.76; p

Table III. Overall nonvertebral fracture rates in published studies (reproduced from Karpf et al.,[33] with permission)

Combined studies[19-23]	Treatment group	Number of patients	No. of patients with fractures	Patient-years at risk	Rate per 100 patient-years	Relative risk: alendronate/placebo (95% CI)
	Placebo	590	60	1347.0	4.45	
	Alendronate	1012	73	2240.3	3.26	0.71 (0.50-0.99)

CI = confidence interval.

<0.05).[32] This result confirmed the results seen in the 5 year extension of the studies by Devogelaer et al.[21] and Tucci et al.[22] i.e. that alendronate 5 mg/day seems as effective as alendronate 10 mg/day as far as the prevention of vertebral and nonvertebral fractures is concerned, during the years 4 and 5.[24]

4.2.2 Height Loss

Height loss should not simply be considered as a surrogate for vertebral deformities, although whether height loss really adds any further information to a vertebral fracture count is unclear. Nevertheless, maintenance of the integrity of body shape is important for the self-esteem of patients, and, as such, height loss is worthwhile reporting. Furthermore, most vertebral fractures are symptomless, while height loss can be appreciable. Height losses of 4.6 and 9.3mm have been reported in the placebo groups and 3.0 and 6.1mm in the treated groups in the studies by Liberman et al.[25] and Black et al.,[26] respectively.[25,26] In the study by Liberman et al.[25] patients with new vertebral fractures lost 23.3mm in height in the placebo group versus 5.9mm in the alendronate group, whereas patients without new vertebral fractures lost 3.3 and 2.8mm in the placebo and alendronate groups, respectively.[25] This underlines the leading part played by vertebral fractures in height loss.

4.2.3 Nonvertebral Fractures

Nonvertebral fractures are frequently of clinical relevance, because most of them necessitate medical intervention. This is in contrast to vertebral fractures in which up to two-thirds of the radiographically-defined fractures are not recognised clinically.[26] In a meta-analysis of published data on all completed prospective, randomised, placebo-controlled trials of alendronate of at least 2 years' duration,[19-23] Karpf et al.[33] have evaluated the preventative effect of alendronate on nonvertebral fractures in postmenopausal women with osteoporosis. Only the results of the l mg/day alendronate treatment arm were not included,[23] because this low dosage did not produce any significant changes in BMD at either site, as compared with placebo. The results are summarised in table III. Among women younger than 65 years old, the nonvertebral fracture rate per 100 patient-years was 3.66 and 2.99 in the placebo and alendronate groups, respectively, whereas for those women aged ≥65 years old, the rates were 5.34 and 3.57, respectively. The ratio of the rates for alendronate versus placebo was consistently less than unity, and even better in elderly patients (0.82 and 0.67, for women <65 and ≥65 years old, respectively). This means that the preventative effect of alendronate on nonvertebral fractures is more marked in the older patients, i.e. the patients most susceptible to fragility fractures.

In the study by Black et al.,[26] all clinical fractures were investigated. The results are summarised

Table IV. Patients with clinical fractures (reproduced from Black et al.,[26] with permission)

	No. of women with at least one fracture (%)		Relative hazard (95% CI)
	placebo	alendronate	
Any clinical fracture[a]	183 (18.2)	139 (13.6)	0.72 (0.58-0.90)
Type of fracture			
Any nonvertebral	148 (14.7)	122 (11.9)	0.80 (0.63-1.01)
Hip	22 (2.2)	11 (1.1)	0.49 (0.23-0.99)
Wrist	41 (4.1)	22 (2.2)	0.52 (0.31-0.87)
Other[b]	99 (9.9)	100 (98)	0.99 (0.75-1.31)

a Including clinical vertebral fracture.

b See section 4.2.3 for detail.

CI = confidence interval.

in table IV. The number of women with clinical fractures at sites other than the spine, hip or wrist (i.e. shoulder, arm, hand, fingers, other small wrist bones, ribs, chest/sternum, pelvis, coccyx/sacrum, leg, ankle, foot/metatarsal, toes and peri-prothetic) was similar in the 2 treatment groups, probably because this heterogeneous group of fractures has variable relationships with low bone mass[34] and with trauma intensity. In the Fosamax International Trial (FOSIT),[35] the preventative effect of alendronate 10 mg/day on the rate of any fractures as well as nonvertebral fractures was already significant after 1 year of therapy (2.2% and 2.0% in patients receiving alendronate versus 4.0% and 3.9% in patients receiving placebo for any fractures and for nonvertebral fractures, respectively).[35]

5. Adverse Effects of Alendronate

5.1 Clinical Adverse Effects Observed in Clinical Trials of at Least 2-Years' Duration

In studies encompassing elderly people, adverse events are rather the rule than the exception, and in the 3 year study by Devogelaer et al.[21] up to 85% of patients experienced 1 or more adverse event. Abdominal pain, back pain, headache and upper respiratory tract infections were the most common adverse events seen in this trial and they occurred at a similar frequency in each of the treatment groups including the placebo group.[21] In this study, upper gastrointestinal adverse events, considered to be possibly drug-related, were equally distributed in all treatment groups.[21] In another study, Tucci et al.[22] found that transient

Table V. Withdrawals from treatment because of drug-related adverse effects (AEs) in published studies

Reference	Drug	Dosage (mg/day)	Withdrawals [no. of patients (%)]	
			general clinical AEs	upper GI AEs
Chesnut et al.[19]	Placebo		NS	0 (0.0)
	Alendronate	5	NS	0 (0.0)
		10	NS	1 (3.3)
		20/5	NS	0 (0.0)
Adami et al.[20]	Placebo		4 (5.6)	4 (5.6)
	Alendronate	5	ND	ND
		10	2 (2.9)	1 (1.5)
		20/5	6 (8.3)	3 (4.2)
Devogelaer et al.[21]	Placebo		4 (2.0)	5 (2.4)
	Alendronate	5	5 (4.8)	5 (4.8)
		10	2 (2.0)	1 (1.0)
		20/5	2 (1.9)	1 (1.0)
Tucci et al.[22]	Placebo		13 (6.8)	3 (1.6)
	Alendronate	5	3 (3.1)	2 (2.0)
		10	5 (5.3)	1 (1.1)
		20/5	7 (7.4)	3 (3.2)
Black et al.[26]	Placebo		96 (9.6)	22 (2.2)[a]
	Alendronate	5	} 78 (7.6)[b]	} NS (1.6)[a]
		10		
Bone et al.[23]	Placebo		9 (9.9)	NS
	Alendronate	5	13 (14.0)	NS
		10	ND	ND
		20/5[c]	ND	ND

a Leading to hospitalisation.

b Values are for both dosages combined.

c Alendronate was given at a dosage of 20 mg/day for 2 years, followed by 5 mg/day thereafter.

ND = no data; **NS =** not stated.

abdominal pain, not leading to discontinuation of the drug, showed a positive trend of frequency across treatment groups (incidence of 10.9%, 15.3%, 20.2%, and 18.1% of the groups receiving placebo, 5 mg/day, 10 mg/day and 20 mg/day for 2 years followed by 5 mg/day, respectively).[22] Flatulence was experienced by some patients and this was also considered to be drug-related.[22]

In another study,[19] a patient receiving alendronate 20 mg/day developed a skin rash that required treatment discontinuation. In this study, severe upper gastrointestinal adverse effects leading to withdrawal of therapy were observed in 11.1% of patients receiving alendronate 40 mg/day versus 3.3% of patients receiving alendronate 10 mg/day.[19] The number and percentages of patients whose reason for withdrawal from treatment was considered to be because of drug-related adverse events, with special emphasis on upper gastrointestinal adverse events, that have been reported in published articles are summarised in table V.

Several abstracts presented at recent meetings have dealt with the gastrointestinal adverse effects of alendronate. In 2347 postmenopausal women enrolled in prevention studies, alendronate 5 mg/day administered for up to 3 years did not provoke more adverse events than placebo, particularly as far as upper gastrointestinal adverse events were concerned.[36] During years 4 and 5, alendronate 5 mg/day, 10 mg/day or 20 mg/day for 2 years followed by 5 mg/day did not provoke more adverse events (drug-related or not) than placebo during years 1 and 2, or placebo and alendronate 10 mg/day during years 4 and 5.[25] In the FIT study, upper gastrointestinal complaints, particularly dyspepsia were common, but alendronate therapy was not associated with an increased incidence of gastric or duodenal adverse effects.[37]

5.2 Laboratory Adverse Experiences in Clinical Trials

In clinical trials, very rarely did the occurrence of laboratory abnormalities lead to withdrawal from treatment. Mild asymptomatic hypocalcaemia was observed in most of the studies. Hypocalcaemia was also dose related but never led to discontinuation of therapy.[21,22] Slight, transient increases in serum glutamic oxaloacetic transaminase levels were observed at a higher frequency in patients receiving alendronate 40 mg/day, but these increases resolved despite continued therapy.[19] In another study,[20] 1 patient receiving alendronate 20 mg/day showed an increase in liver enzyme levels and this led to withdrawal from treatment. A decrease in leucocyte count was observed in 1 patient receiving alendronate 5 mg/day and this led to discontinuation of the drug,[21] whereas increases in lymphocyte count (2.9% of patients) and in urine casts (3.1% of patients) occurred more frequently in patients treated with alendronate 20 mg/day for 2 years followed by 5 mg/day than placebo (0% of patients).[21] Eosinophilia led to treatment discontinuation in 1 patient receiving alendronate 20 mg/day.[20]

5.3 Histomorphometry in Clinical Trials

Around 400 biopsies of which >200 were obtained from patients enrolled in the primary phase III studies have been assessed by histomorphometric evaluation.[8] Alendronate taken at any dosage up to 20 mg/day produced normal mineralisation with no signs of overt or focal osteomalacia during a therapy lasting for up to 3 years.[8]

5.4 Biological Parameters of Bone Turnover in Clinical Trials

Not unexpectedly, a decrease in bone turnover was observed with alendronate treatment in all studies. This proved to be true both for markers of bone resorption (e.g. urinary excretion of deoxypyridinoline) and for markers of bone formation (e.g. serum alkaline phosphatase).[21] The effects of alendronate on parameters of bone turnover indicate that a new steady state of bone turnover was achieved 3 to 6 months after the start of therapy, with no further decrease observed beyond that period. There is, therefore, no result suggestive of frozen bone.

5.5 Post-Marketing Information

In trials of alendronate,[19-23] the overall incidence of adverse upper gastrointestinal adverse events was similar in patients receiving placebo and those receiving any alendronate regimen. However, it is well known that aminobisphosphonates may provoke oesophagitis.[12]

After a preliminary published report,[38] the postmarketing data through to March 1996 comprised reports of adverse events related to the oesophagus in 199 patients out of 475 000 patients exposed to alendronate (i.e. 4.19 per 10 000 patients); 32 (16%) of these patients were hospitalised.[39] In most of the patients, oesophageal complications occurred during the first month of alendronate administration. In 61% of patients with available adequate information about how to take alendronate, the alendronate tablets had been taken incorrectly. Endoscopic findings in the published cases were consistent with a chemical cause.[38-42] This complication has also been described with the 5mg dose,[38,40] as well as with other formulations of alendronate.[43] The exact mechanism is unknown, but oesophagitis may be caused by a local reaction of the mucosa to contact with the concentrated drug since the occurrence of oesophagitis is uncommon with intravenous administration.[44] Calcium chelation and the presence of acid are not a predominant mechanism of bisphosphonate-induced oesophageal damage.[44]

6. Other Therapies for Osteoporosis

Currently, a number of therapies are available for the prevention and treatment of osteoporosis. However, in published clinical trials thus far, alendronate 5 to 10 mg/day is the only drug with proven efficacy on both symptomatic and radiographically-defined vertebral fracture as well as nonvertebral fracture, and postmenopausal osteoporosis with or without prevalent fracture. It is possible that alendronate 10mg produces protection against fractures more rapidly than alendronate 5mg.[35] However, this remains to be confirmed. Only 1 other study, in which patients received calcium 1200 mg/day and vitamin D 800 IU/day supplementation, has shown a reduction by about 30% in the risk of hip and other non-axial fractures among elderly women in nursing homes; the vast majority of these women were vitamin D-deficient.[45,46] However, this kind of therapy has its efficacy probably limited to a very targeted population living in retirement homes. A comparable study performed in The Netherlands in a similar population, but providing only supplementation with vitamin D 400 IU/day failed to show any significant action on incident fractures.[47]

The preventative effect of estrogen hormone replacement therapy (HRT) on bone loss has been known for years.[48-51] However, to date, no prospective randomised trials have been conducted to demonstrate that HRT possesses a preventative effect on fractures. However, a 1-year study in a few patients has shown such an effect.[52] This is to be compared to the duration necessary to demonstrate any effect in most of the alendronate studies, i.e. 2 to 3 years.[25,26] Whether HRT is more rapidly active on incident fractures, owing to its combined skeletal and extraskeletal impact, as opposed to the restricted osseous impact of bisphosphonates, remains to be demonstrated. Notwithstanding the lack of prospective data, several retrospective studies tend to demonstrate a protective efficacy on fracture incidence for HRT, if it is administered for at least 5 years.[53] Along with definite extraskeletal advantages,[54-56] HRT does have some drawbacks, potentially limiting its use. First, bone loss resumes immediately after HRT is discontinued,[57] contrary to the effect of bisphosphonates,[58-61] and therefore the protective effect of HRT might be lost after a while.[62] Second, there is serious concern about the incidence of breast cancer after prolonged use of HRT.[63,64]

Fluoride salts are able to increase trabecular bone mass during administration.[65,66] Their preventative effect on fracture is limited to the axial skeleton,[67,68] and they do not have any protective (or deleterious) action on the hip fracture rate, even if taken as directed.[66]

Cyclical intermittent etidronate is commonly used worldwide for osteoporosis; however, it is not available in the US. In a 3-year, double-blind study, cyclical intermittent etidronate was shown to significantly reduce the fracture rate after 2 years.[69] However, during the third year of the study, the number of fractures in patients receiving active therapy nearly doubled, so that, finally, the effect on the vertebral fracture rate was no longer significant,[70] and no patent effect on the nonvertebral fracture rate was observed.[70] Moreover, there is some concern with regard to bone quality,[5,6] even if no clinically relevant consequence has been so far reported. Furthermore, alendronate can increase BMD at the spine and hip in women with postmenopausal osteoporosis who fail to respond to intermittent cyclic etidronate.[71] Changes in bone markers suggest that alendronate causes less inhibition of bone formation and more complete suppression of bone resorption than etidronate.[71] In my opinion, these data underline the therapeutic superiority of alendronate.

Calcitonin has been shown to be protective against vertebral fractures in some small trials.[72,73] Recently, an interim analysis of a large study has shown that intranasal salmon calcitonin reduces the relative risk of new vertebral fractures compared with placebo at 3 years by 16.2, 37.4 and 16.0% for the 100, 200 and 400 IU/day treatment groups, respectively.[74]

In a comparative study of calcitriol and calcium in postmenopausal women, the rates of vertebral fractures appeared to be lower in the calcitriol group than in the calcium group.[75] However, these data should be interpreted with caution, owing to the dramatic, and rather unexpected, increase in the fracture rate in the calcium group.[75]

7. How Should Alendronate be Used in Clinical Practice?

Some hospitalisations for patients with osteoporosis occur as a direct result of fractures, especially those of the hip, which cause the major part of the healthcare expenditures related to osteoporosis. Based on the FIT study, it has been calculated that there was a 20% reduction in all-cause hospitalisations in favour of alendronate (12.1 hospitalisations per 100 patient-years for placebo versus 9.7 for alendronate group; $p = 0.001$).[76] This reduction was only partly attributable to hospitalisations resulting from the fracture event. Hospitalisations not directly related to a fracture were reduced by 17.6% by alendronate ($p = 0.014$).[76] According to the authors, it seemed that fractures that came to clinical attention were harbingers of an increased risk for subsequent all-cause hospitalisation by a so far unexplained mechanism.

These decreased numbers of hospitalisations could possibly justify prophylactic prescription of alendronate in elderly populations. In a post-hoc analysis of data from the FIT study,[26] it has been shown that treatment with alendronate was effective in reducing the risk of fracture in postmenopausal women with advanced osteoporosis, as evidenced by very low BMD, multiple pre-existing radiographic vertebral fractures, or history of postmenopausal fracture.[77] A direct comparison of the presumed preventative, but not statistically significant, action of etidronate on the vertebral fracture rate[69,70] with the largely demonstrated preventative action of alendronate on the fracture risk can therefore only be speculative. Moreover, as with etidronate, there are only scant data on its effect on the rate of nonvertebral fractures, which tend to be the most expensive. Unlike the re-analysis of the etidronate study which encompasses very few patients with low bone mass and vertebral fractures,[70] the vertebral fracture arm of the FIT study is large enough to examine the effect of alendronate across different categories of fracture risk and to demonstrate a reduction in the risk of incident clinical fractures.[77] According to the authors,[77] only 4 women with 2 or more prevalent vertebral fractures need to be treated with alendronate for 5 years in order to prevent 1 vertebral fracture compared with 16 women with 1 existing vertebral fracture. Similarly and, maybe more importantly, only 6 women with 2 or more existing vertebral fractures need to be treated with alendronate for 5 years compared with 26 women with 1 prevalent vertebral fracture in order to prevent 1 clinical fracture. In

the case of limited financial resources, these very-high-risk women should be prioritised for alendronate therapy, because they will get the greatest benefit of treatment as far as the risk of future fractures is concerned.

8. Conclusions

Theoretically, the alkylamino structure of alendronate could predispose it to producing an acute phase–like reaction. This has not been observed with oral alendronate and seems limited to the intravenous route.[78,79] The fear of developing frozen bone has been dismissed by the data on biological remodelling parameters[8] and the bone histomorphometry results.[8]

The effects of alendronate in increasing BMD were similar in a wide variety of patient subgroups regardless of age, race, baseline rate of bone turnover or baseline BMD.[21] Moreover, alendronate exerted positive effects on both trabecular and cortical sites, whereas no other therapeutic agent has thus far been reported to produce consistently significant increases in bone mass at cortical sites, with a positive effect on the reduction of both vertebral and hip fractures.[26]

Increases in BMD with alendronate were particularly rapid during the first year of treatment, consistent with an acute inhibition of bone resorption, allowing the filling of the remodelling spaces.[80] The continued, albeit less marked, gains in BMD during the third treatment years suggest that long term therapy with alendronate may reverse the imbalance between bone resorption and bone formation observed in postmenopausal osteoporosis. This might be explained by a nocturnal increase in parathyroid hormone secretion which could mimic the anabolic effect of low-dose intermittent parathyroid hormone administration to stimulate bone formation.[81] An alternative explanation could be a further degree of mineralisation at the level of the osteons related to the decrease in bone turnover, allowing a prolongation of the formation period in the bone remodelling cycle,[82] a process potentially leading to prematurely aged bone. Only quantitative microradiographical studies of bone biopsy specimens could dismiss such an hypothesis.[82] Whatever the mechanisms, the gain in BMD seems to level off after the fourth year of alendronate therapy.[24]

Skin rashes may be of clinical relevance with bisphosphonates, as this has been as shown by in 1 patient receiving tiludronate therapy.[17] In at least 2 patients receiving alendronate, who developed a skin rash, rash was considered to fulfil criteria for drug related.[8]

Very few laboratory abnormalities have been recorded in clinical trials of alendronate. Mild hypocalcaemia was always asymptomatic, and might be a prerequisite for the anabolic action of alendronate.[81] No case of secondary or tertiary hyperparathyroidism has so far been observed, notwithstanding the long term stimulation of parathyroid hormone secretion.

The most significant adverse effect of alendronate consists of its oesophageal toxicity, leading to chemical oesophagitis in around 1% of patients receiving alendronate. In most cases, the adverse events were associated with poor compliance with the recommended instructions for administration, including failure to stop medication after the appearance of suggestive symptoms and use of alendronate in patients with pre-existing oesophageal disorders. Thus, with better compliance to the recommended instructions, and avoidance in patients with risk factors for oesophageal disorders the number of cases of chemical oesophagitis should decrease, if not be completely suppressed.[83] This potentially dangerous complication of alendronate should not, however, counterbalance the positive effects of this agent on the prevention of osteoporosis fractures and the pain, loss of autonomy, loss of self-esteem, depression,[84] and even death, associated with such fractures.

Addendum

After the acceptance of this paper, 2 articles on the prevention of bone loss in non-osteoporotic postmenopausal women with alendronate have been published.[85,86] In these studies, postmeno-

pausal women under 60 years of age (age range 40 to 50 years) were studied. In the first study, 1499 women who had been postmenopausal for at least 6 months received alendronate 2.5, 5 mg/day or placebo for 2 years and 110 received estrogen plus progestin therapy.[85] In the second study, 457 women who had experienced menopause 6 to 36 months before enrolment received either placebo or alendronate 1, 5 or 10 mg/day, for 3 years or alendronate 20 mg/day for 2 years followed by placebo during the third year.[86] In both studies, placebo groups lost bone significantly at the lumbar spine, at the hip and whole body bone mineral density decreased. Alendronate 1 mg/day significantly attenuated, but did not fully prevent, bone loss. Alendronate 2.5 mg/day provoked a less marked increase in bone mass, less marked than the 5 mg/day dosage, which in turn induced less gain in BMD than the 10 mg/day dosage. The bone mineral density changes at 24 months in the group who received alendronate 20 mg/day for 2 years followed by placebo during the third year were similar to those in the 5 and 10 mg/day groups. Interestingly enough, after 24 months, when women in the 20 mg/day group were switched to placebo, loss of bone density resumed at a rate similar to that seen throughout the entire study in the placebo groups.[86]

Estrogen plus progestin therapy provoked bone gains after 2 years that were slightly higher than those in patients receiving alendronate 2.5 and 5 mg/day. No patients developed oesophagitis in the 1, 2.5, 5 and 10 mg/day alendronate groups, whereas 1 woman in the 20 mg/day group did. As the incidence of odynophagia was significantly increased in the 10 and 20 mg/day groups, and since the 5 mg/day dosage was associated with a smaller proportion of patients who lost more than 2% of bone mineral density after 2 years as compared with the 2.5 mg/day dosage at the spine, at the hip and total body bone mineral density, 5 mg/day seems to be the optimal dosage for the prevention of bone loss in postmenopausal women.[85,86]

Alendronate should, however, not be considered as the first choice for osteoporosis prevention in women whose bone mass is in the upper half of the bone mass distribution of normal or who are willing to receive HRT. Bisphosphonate protection should be restricted to women with a low bone mass and who cannot receive HRT, owing to contraindications.[87]

References

1. Consensus development conference. Diagnosis, prophylaxis, and treatment of osteoporosis. Am J Med 1993 Jun; 94 (6): 646-50
2. Melton LJ III, Chrischilles EA, Cooper C, et al. Perspective: how many women have osteoporosis? J Bone Miner Res 1992 Sep; 7 (9): 1005-10
3. Jensen GF, Christiansen C, Boesen J, et al. Epidemiology of postmenopausal spinal and long bone fractures. Clin Orthop 1982 Jun; 166: 75-81
4. Fleisch H, Russell RGG, Francis MD. Diphosphonates inhibit hydroxyapatite dissolution *in vitro* and bone resorption in tissue culture and *in vivo*. Science 1969 Sep 19; 165 (899): 1262-4
5. Axelrod D, Teitelbaum SL. Results of long term cyclical etidronate therapy: bone histomorphometry and clinical correlates [abstract]. J Bone Miner Res 1994 Aug; 9 Suppl. 1: S136
6. Wimalawansa SJ. Combined therapy with estrogen and etidronate has an additive effect on bone mineral density in the hip and vertebrae: four-year randomized study. Am J Med 1995 Jul; 99 (1): 36-42
7. Balena R, Markatos A, Seedor JG, et al. Long-term safety of the aminobisphosphonate alendronate in adult dogs. II – Histomorphometric analysis of the L5 vertebrae. J Pharmacol Exp Ther 1996 Jan; 276 (1): 277-83
8. Daifotis AG, Karpf DB. Summary of safety profile and future research with alendronate. Br J Rheumatol 1997 Jun; 36 Suppl. 1: 20-3
9. Fleisch H. Bisphosphonates in bone disease. New York: Parthenon, 1995
10. Schenk R, Eggli P, Fleisch H, et al. Quantitative morphometric evaluation of the inhibitory activity of new aminobisphosphonates on bone resorption in the rat. Calcif Tissue Int 1986 Jun; 38 (6): 342-9
11. Schweitzer DH, Oostendorp-Van De Ruit M, Van Der Pluijm G, et al. Interleukin-6 and the acute phase response during treatment of patients with Paget's disease with the nitrogen-containing bisphosphonate dimethylamino-hydroxypropylidene bisphosphonate. J Bone Miner Res 1995 Jun; 10 (6): 956-62
12. Lufkin EG, Argueta R, Whitaker MD, et al. Pamidronate: an unrecognized problem in gastrointestinal tolerability. Osteoporosis Int 1994 Nov; 4 (6): 320-2
13. Balena R, Toolan BC, Shea M, et al. The effects of 2-year treatment with the aminobisphosphonate alendronate on bone metabolism, bone histomorphometry, and bone strength in ovariectomized nonhuman primates. J Clin Invest 1993 Dec; 92 (6): 2577-86
14. Lafage M-H, Balena R, Battle MA, et al. Comparison of alendronate and sodium fluoride effects on cancellous and cortical bone in minipigs. A one year study. J Clin Invest 1995 May; 95 (5): 2127-33
15. Peter CP, Guy J, Shea M, et al. Long-term safety of the aminobisphosphonate alendronate in adult dogs. I. General safety and biomechanical properties of bone. J Pharmacol Exp Ther 1996 Jan; 276 (1): 271-6

16. Lin JH, Duggan DE, Chen IW, et al. Physiological disposition of alendronate, a potent anti-osteolytic bisphosphonate, in laboratory animals. Drug Metab Dispos 1991 Sep-Oct; 19 (5): 926-32
17. Roux C, Listrat V, Villette B, et al. Long-lasting dermatological lesions after tiludronate therapy. Calcif Tiss Int 1992 Apr; 50 (4): 378-80
18. Gertz BJ, Holland SD, Kline WF, et al. Studies of the oral bioavailability of alendronate. Clin Pharmacol Ther 1995 Sep; 58 (3): 288-98
19. Chesnut CH III, McClung MR, Ensrud KE, et al. Alendronate treatment of the postmenopausal osteoporotic woman: effect of multiple dosages on bone mass and bone remodelling. Am J Med 1995 Aug; 99 (2): 144-52
20. Adami S, Passeri M, Ortolani S, et al. Effects of oral alendronate and intranasal salmon calcitonin on bone mass and biochemical markers of bone turnover in postmenopausal women with osteoporosis. Bone 1995 Oct; 17 (4): 383-90
21. Devogelaer JP, Broll H, Correa-Rotter R, et al. Oral alendronate induces progressive increases in bone mass of the spine, hip, and total body over 3 years in postmenopausal women with osteoporosis. Bone 1996 Feb; 18 (2): 141-50
22. Tucci JR, Tonino RP, Emkey RD, et al. Effect of three years of oral alendronate treatment in postmenopausal women with osteoporosis. Am J Med 1996 Nov; 101 (5): 488-501
23. Bone HG, Downs RW, Tucci JR, et al. Dose-response relationships for alendronate treatment in osteoporotic elderly women. J Clin Endocrinol Metab 1997 Jan; 82 (1): 265-74
24. Favus M, Emkey R, Leite M, et al. Five-year treatment of osteoporosis in postmenopausal women with oral alendronate: effects on bone mass and turnover and safety [abstract]. J Bone Miner Res 1997 Aug; 12 Suppl. 1: S150
25. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. N Engl J Med 1995 Nov 30; 333 (22): 1437-43
26. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 1996 Dec 7; 348 (9041): 1535-41
27. WHO Study Group. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. World Health Organ Tech Rep Ser 1994; 843: 1-129
28. Minne HW, Leidig G, Wuster C, et al. A newly developed spine deformity index (SDI) to quantitate vertebral crush fractures in patients with osteoporosis. Bone Miner 1988 Mar; 3 (4): 335-49
29. Ross PD, Davis JW, Epstein RS, et al. Pre-existing fractures and bone mass predict vertebral fracture incidence in women. Ann Intern Med 1991 Jun 1; 114 (11): 919-23
30. Aspray TJ, Prentice A, Cole TJ, et al. Low bone mineral content is common but osteoporotic fractures are rare in elderly rural Gambian women. J Bone Miner Res 1996 Jul; 11 (7): 1019-25
31. Wells G, Cranney A, Shea B, et al. Responsiveness of endpoints in osteoporosis clinical trials. J Rheumatol 1997 Jun; 24 (6): 1230-3
32. Cummings SR, Black DM, Thompson DE, for the FIT Research Group. Alendronate reduces the risk of vertebral fractures in women without pre-existing vertebral fractures: results of the fracture intervention trial [abstract]. J Bone Miner Res 1997 Aug; 12 Suppl. 1: S149
33. Karpf DB, Shapiro DR, Seeman E, et al. Prevention of nonvertebral fractures by alendronate. A meta-analysis. JAMA 1997 Apr 9; 277 (14): 1159-64
34. Seeley DG, Browner WS, Nevitt MC, et al. Which fractures are associated with low appendicular bone mass in elderly women? Ann Intern Med 1991 Dec 1; 115 (11): 837-42
35. Pols HAP for the FOSIT Study Group. A multinational, placebo-controlled study of alendronate in postmenopausal women with osteoporosis [abstract]. Results from the FOSIT study. J Bone Miner Res 1997 Aug; 12 Suppl. 1: S172
36. McClung M, Wasnich R, Hosking D, et al. Safety of oral alendronate 5 mg in osteoporosis prevention [abstract]. J Bone Miner Res 1997 Aug; 12 Suppl. 1: S469
37. Bauer DC, Thompson D, Black DM, et al. Alendronate use is not associated with gastric or duodenal side effects: the fracture intervention trial (FIT) [abstract]. J Bone Miner Res 1997 Aug; 12 Suppl. 1: S468
38. Maconi G, Porro GB. Multiple ulcerative esophagitis caused by alendronate. Am J Gastroenterol 1995 Oct; 90 (10): 1889-90
39. De Groen PC, Lubbe DF, Hirsch LJ, et al. Esophagitis associated with the use of alendronate. N Engl J Med 1996 Oct 3; 335 (14): 1016-21
40. Sorrentino D, Trevisi A, Bernardis V, et al. Esophageal ulceration due to alendronate [letter]. Endoscopy 1996 Aug; 28 (6): 529
41. Rimmer DE, Rawls DE. Improper alendronate administration and a case of pill esophagitis. Am J Gastroenterol 1996 Dec; 91 (12): 2648-9
42. Naylor G, Davies MH. Oesophageal stricture associated with alendronic acid. Lancet 1996 Oct 12; 348 (9033): 1030-1
43. Adami S, Zamberlan N. Adverse effects of bisphosphonates: a comparative review. Drug Saf 1996 Mar; 14 (3): 158-70
44. Blank MA, Ems BL, Gibson GW, et al. Nonclinical model for assessing gastric effects of bisphosphonates. Dig Dis Sci 1997 Feb; 42 (2): 281-8
45. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D_3 and calcium to prevent hip fractures in the elderly women. N Engl J Med 1992 Dec 3; 327 (23): 1637-42
46. Chapuy MC, Arlot ME, Delmas PD, et al. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. BMJ 1994 Apr 23; 308 (6936): 1081-2
47. Lips P, Graafmans WC, Ooms ME, et al. Vitamin D supplementation and fracture incidence in elderly persons. A randomized, placebo-controlled clinical trial. Ann Intern Med 1996 Feb 15; 124 (4): 400-6
48. Lindsay R, Hart DM, Aitken JM, et al. Long-term prevention of postmenopausal osteoporosis by oestrogen. Evidence for an increased bone mass after delayed onset of oestrogen treatment. Lancet 1976 May 15; 1 (7968): 1038-41
49. Christiansen C, Christensen MS, Transbol I. Bone mass in postmenopausal women after withdrawal of oestrogen/gestagen replacement therapy. Lancet 1981 Feb 28; 1 (8218): 459-61
50. Wimalawansa SJ. Use of plasma 17 β-estradiol as a guideline for parenteral administration of estrogen for the prevention and treatment of osteoporosis. In: Christiansen C, Overgaard K, editors. Osteoporosis 1990; Handelstrykkeriet, Aalborg: Osteopress ApS, 1990: 1917-22
51. Hassager C, Jensen SB, Christiansen C. Non-responders to hormone replacement therapy for the prevention of postmenopausal bone loss: do they exist? Osteoporosis Int 1994 Jan; 4 (1): 36-41
52. Lufkin EG, Wahner HW, O'Fallon WM, et al. Treatment of postmenopausal osteoporosis with transdermal estrogen. Ann Intern Med 1992 Jul 1; 117 (1): 1-9
53. Paganini-Hill A, Ross RK, Gerkins VR, et al. Menopausal estrogen therapy and hip fractures. Ann Intern Med 1981 Jul; 95 (1): 28-31
54. Bush TL. Extraskeletal effects of estrogen and the prevention of atherosclerosis. Osteoporosis Int l991 Oct; 2 (1): 5-11
55. Paganini-Hill A, Ross RK, Henderson BE. Postmenopausal oestrogen treatment and stroke: a prospective study. BMJ 1988 Aug 20-27; 297 (6647): 519-22

56. Gangar KF, Vyas S, Whitehead M, et al. Pulsatility index in internal carotid artery in relation to transdermal oestradiol and time since menopause. Lancet 1991 Oct 5; 338 (8771): 839-42
57. Lindsay R, Hart DM, MacLean A, et al. Bone response to termination of oestrogen treatment. Lancet 1978 Jun 24; 1 (8078): 1325-7
58. Devogelaer JP, Triki R, Depresseux G, et al. Remnant effect of pamidronate on bone metabolism in osteoporosis [abstract]. J Bone Miner Res 1994 Aug; 9 Suppl. 1: S329
59. Landman JO, Hamdy NAT, Pauwels EKJ, et al. Skeletal metabolism in patients with osteoporosis after discontinuation of long-term treatment with oral pamidronate [abstract]. Bone 1995 Dec; 17 (6): 615
60. Orr-Walker B, Wattie DJ, Evans MC, et al. Effects of prolonged bisphosphonate therapy and its discontinuation on bone mineral density in post-menopausal osteoporosis. Clin Endocrinol 1997 Jan; 46 (1): 87-92
61. Stock JL, Bell NH, Chesnut CH III, et al. Increments in bone mineral density of the lumbar spine and hip and suppression of bone turnover are maintained after discontinuation of alendronate in postmenopausal women. Am J Med 1997 Oct; 103: 291-7
62. Felson DT, Zhang Y, Hannan MT, et al. The effect of postmenopausal estrogen therapy on bone density in elderly women. N Engl J Med 1993 Oct 14; 329 (16): 1141-6
63. Bergkvist L, Adami HO, Persson I, et al. The risk of breast cancer after estrogen and estrogen-progestin replacement. N Engl J Med 1989 Aug 3; 321 (5): 293-7
64. Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. N Engl J Med 1995 Jun 15; 332 (24): 1589-93
65. Riggs BL, Hodgson SF, O'Fallon WM, et al. Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. N Engl J Med 1990 Mar 22; 322 (12): 802-9
66. Nagant de Deuxchaisnes C, Devogelaer JP. Restorative therapy of osteoporosis. In: Broll H, Dambacher MA, editors. Osteoporosis: a guide to diagnosis and treatment. Basel: Karger, 1996, 18: 207-64
67. Mamelle N, Meunier PJ, Dusan R, et al. Risk-benefit ratio of sodium fluoride treatment in primary vertebral osteoporosis. Lancet 1988 Aug 13; 2 (8607): 361-5
68. Pak CY, Sakhaee K, Adams-Huet B, et al. Treatment of postmenopausal osteoporosis with slow-release sodium fluoride. Final report of a randomized controlled trial. Ann Intern Med 1995 Sep 15; 123 (6): 401-8
69. Watts NB, Harris ST, Genant HK, et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. N Engl J Med 1990 Jul 12; 323 (2): 73-9
70. Harris ST, Watts NB, Jackson RD, et al. Four-year study of intermittent cyclic etidronate treatment of postmenopausal osteoporosis: three years of blinded therapy followed by one year of open therapy. Am J Med 1993 Dec; 95 (6): 557-67
71. Watts NB, Becker P. Alendronate increases bone mineral density at spine and hip in women with postmenopausal osteoporosis who fail to respond to intermittent cyclic etidronate [abstract]. J Bone Miner Res 1997 Aug; 12 Suppl. 1: S171
72. Rico H, Hernandez ER, Revilla M, et al. Salmon calcitonin reduces vertebral fracture rate in postmenopausal crush fracture syndrome. Bone Miner 1992 Feb; 16 (2): 131-8
73. Overgaard K, Hansen MA, Jensen SB, et al. Effect of salcatonin given intranasally on bone mass and fracture rates in established osteoporosis: a dose-response study. BMJ 1992 Sep 5; 305 (6853): 556-61
74. Stock JL, Avioli LV, Baylink DJ, et al. Calcitonin-salmon nasal spray reduces the incidence of new vertebral fractures in postmenopausal women: three-year interim results of the PROOF study [abstract]. J Bone Miner Res 1997 Aug; 12 Suppl. 1: S149
75. Tilyard MW, Spears GFS, Thomson J, et al. Treatment of postmenopausal osteoporosis with calcitriol or calcium. N Engl J Med 1992 Feb 6; 326 (6): 357-62
76. Thompson DE, Cummings S, Black D, et al. Clinical (symptomatic) fractures are predictors of all-cause hospitalization [abstract]. J Bone Miner Res 1997 Aug; 12 Suppl. 1: S144
77. Ensrud KE, Black DM, Palermo L, et al. Treatment with alendronate prevents fractures in women at highest risk. Results from the Fracture Intervention Trial. Arch Intern Med 1997 Dec; 157 (22): 2617-24
78. Vasikaran SD, Khan S, McCloskey EV, et al. Sustained response to intravenous alendronate in postmenopausal osteoporosis. Bone 1995 Dec; 17 (6): 517-20
79. Adami S, Fossaluzza V, Gatti D, et al. Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. Ann Rheum Dis 1997 Mar; 56 (3): 201-4
80. Heaney RP. The bone remodeling transient: implications for the interpretation of clinical studies of bone mass change. J Bone Miner Res 1994 Oct; 9 (10): 1515-23
81. Greenspan SL, Holland S, Maitland-Ramsey L, et al. Alendronate stimulation of nocturnal parathyroid hormone secretion: a mechanism to explain the continued improvement in bone mineral density accompanying alendronate therapy. Proc Assoc Am Phys 1996 May; 108 (3): 230-8
82. Chavassieux PM, Arlot ME, Reda C, et al. Histomorphometric assessment of the long-term effects of alendronate on bone quality and remodeling in patients with osteoporosis. J Clin Invest 1997 Sep; 100 (6): 1475-80
83. Graham DY, Malaty HM, Goodgame R. Primary aminobisphosphonates: a new class of gastrotoxic drugs. Comparison of alendronate and aspirin. Am J Gastroenterol 1997; 92 (8): 1322-5
84. Gold DT. The clinical impact of vertebral fractures: quality of life in women with osteoporosis. Bone 1996 Mar; 18 (3) Suppl.: 185S-9S
85. Hosking D, Chilvers CED, Christiansen C, et al. Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. N Engl J Med 1998 Feb 19; 338 (8): 485-92
86. McClung M, Clemmesen B, Daifotis A, et al. Alendronate prevents bone loss in women without osteoporosis. A double-blind, randomized, controlled trial. Ann Intern Med 1998 Feb 15; 128 (4): 253-61
87. Heaney RP. Bone mass, bone loss, and osteoporosis prophylaxis. Ann Intern Med 1998 Feb 15; 128 (4): 313-4

Correspondence and reprints: Dr *Jean-Pierre Devogelaer*, Department of Rheumatology, UCL 5390 St-Luc University Hospital, Ave Hippocrate 10 B-1200 Brussels, Belgium.
E-mail: Devogelaer@ruma.ucl.ac.be