Differences in persistence, safety and efficacy of generic and original branded once weekly bisphosphonates in patients with postmenopausal osteoporosis: 1-year results of a retrospective patient chart review analysis

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Differences in persistence, safety and efficacy of generic and original branded once weekly bisphosphonates in patients with postmenopausal osteoporosis – 1-year results of a retrospective patient chart review analysis

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Abstract:

Objective: To compare the changes on bone mineral density, the effects on persistence and adverse events, in patients treated for postmenopausal osteoporosis with either generic alendronate or with branded alendronate (Fosamax®) or branded risedronate (Actonel®) once weekly. Patients and methods: In this retrospective patient chart analysis we reviewed the one year observational treatment results of 186 women (ITT population) with postmenopausal osteoporosis. Patients from our out-patient department having started with once weekly bisphosphonate therapy between 36 to at least 12 months before this chart review were included in this comparative three arm study according to their treatment: A: Generic Alendonate 70 mg products, B: Branded Alendronate (Fosamax®) 70 mg once weekly and C: Branded Risedronate (Actonel®) 35 mg once weekly. All patients received basic therapy with 1200 mg calcium and 800 IU Vitamin D per day. Patient's bone mineral density (BMD) at lumbar spine and total hip was below – 2.5 T-score, and they were with or without prevalent vertebral and non-vertebral fractures. Results: Data analysis of the 186 patient's shows an average increase in LS-BMD after 12 months of 2.8%, 5.2% and 4.8% for the groups A, B and C respectively. The respective mean changes at total hip were 1.5%, 2.9%, and 3.1%. At both sites, the mean increases in BMD were not different between the two groups receiving branded bisphosphonates (B, C) but for both were significantly higher than for the group treated with generic alendronate (A). At 12 months 68% of group A, 84% of group B and 94% of group C were still on bisphosphonate therapy. The persistence of patients treated with generic alendronate was significantly lower as compared to each of the two with branded bisphosphonates treated groups. The total number of patients reporting gastrointestinal adverse events were 32, 15 and 9 for group A, group B and group C respectively. Conclusions: Significantly lower increases of lumbar spine and total hip BMD with generic alendronate once weekly as compared to the two branded bisphosphonate originals (Fosamax®, Actonel®) were observed. The reasons for the 40-50% lower BMD increase rates when using the generic compounds are not know yet. At least in part the lower efficacy can be explained by a significantly lower degree of persistence with

generic alendronate, which could be related to a higher incidence of gastrointestinal adverse events. Other reasons could be lower bioavailability or potency of generic alendronate.

Key words

Generic alendronate; branded bisphosphonates; risedronate; persistence; adverse events; efficacy.

Figure legends:

Figure 1: Persistence with bisphosphonate therapy and Calcium/Vitamin D supplementation (% patients at month 12).

Figure 2: Mean percent changes in lumbar spine (LS) and total hip (TH) after 12 months.

Table legends:

Table 1: Baseline characteristics of patients.

Table 2: Persistence with bisphosphonate therapy and Calcium/Vitamin D supplementation at month 12.

Table 3: Number of patients with gastrointestinal adverse events during the 12 months follow-up period.

Table 4: Number of patients with non-gastrointestinal adverse events during the 12 months follow-up period.

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Introduction

Osteoporosis is an important and very frequent chronic disease

Osteoporosis is a very common skeletal disease in aging populations and accordingly listed by the WHO and UNO among the 10 most important and most frequent chronic diseases of mankind [1,2]. It is a progressive skeletal pathology characterised by loss of bone mass and quality and development of brittle bones that results in increased risk of fractures. The estimated worldwide number of new osteoporotic fractures for the year 2000 was 9.0 million, of which 1.6 million were at the hip, 1.7 million were at the distal forearm and 1.4 million were clinical vertebral fractures [3]. Osteoporotic fractures have extensive clinical and economic consequences, and are a major public health concern. The important burden of osteoporotic fractures highlights the need for osteoporosis therapies with established high efficacy.

Bisphosphonates are the most common therapy for osteoporosis

Treatment options for osteoporosis have substantially improved in recent years [1,2,4-6]: appropriate antiresorptive or anabolic medications are available to prevent future fractures. Bisphosphonates inhibit osteoclast activity. Bisphosphonates are today's worldwide leading medication [7-16] and are recommended as first-line treatments for osteoporosis [1,2,17,18]. Two chemically distinct groups of bisphosphonates exist: Simple non-nitrogen-containing bisphosphonates (Non-N-BP's, e.g., Etidronate) and nitrogen-containing bisphosphonates (N-BP´s) e.g., Ibandronate, Alendronate, Zoledronate and Risedronate). There are two fundamentally, distinct components of the mechanism of action of nitrogen containing bisphosphonates (N-BPs) [19,20]: These are 1) binding to the bone, and 2) binding to and inhibition of a key osteoclast enzyme farnesyl pyrophosphate synthase (FPPS). Regarding the oral bisphosphonates, only Risedronate and Alendronate have been proven to reduce vertebral and hip fracture risk in clinical trials [8-15,21-24]. Zoledronate is an intravenous bisphosphonate therapy and has also been proven to reduce vertebral and hip fracture risk in clinical trials.

The importance of compliance, persistence and adherence for optimal therapeutic results

The therapeutic aim of reducing the risk of fractures requests a persistent intake of a effective long-term medication [1,2]. The effectiveness of a treatment however, depends not only on the efficacy of the used medication but also on persistent drug intake of patients [25-28]. Drugs do not work in patients who do not take them. Compliance is basically adherence to a drug regimen as in taking medications correctly and on time. It can be defined as the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen. Compliance is usually measured over a period of time and reported as a percentage [29]. Compliance differs from persistence, which is defined as the duration of time from initiation to discontinuation of therapy. Persistence addresses how long a patient remains on therapy and it ends as soon as a patient stops taking a specified drug for a prolonged period of time. Adherence is the combination of compliance and persistence. Compliance, persistence and adherence are crucial to achieve also in patients real daily life situation the optimal therapeutic results demonstrated in clinical trials.

Introduction of generic bisphosphonates

During the last years an increasing number of generic alendronates were introduced based on bioequivalence data in numerous countries. Insurances and Health Care Providers increased pressure on physicians to prescribe mainly generic alendronate instead of branded original bisphosphonates like Fosamax® (Alendronate) and Actonel® (Risedronate). Little is known however about the provenience and quality of the still increasing number of generic Alendronates and clinical trials or observational postmarketing studies on bone mineral density and fracture efficacy, adverse events and compliance or persistence with these new “Alendronic acids” initiatives were never performed. This is an important gap of knowledge and means today physicians in many countries are supposed to prescribe mainly these cheaper generic Alendronates and at the same time they are unaware of the manufacturer of the respective compounds and whether efficacy and safety are really the same as were demonstrated for the original branded oral bisphosphonates in clinical or real practice studies. Also a higher rate of adverse events with generic Alendronates has often related from daily practice but only one study from Canada was published demonstrating indeed a higher incidence in gastro-intestinal side effects in patients

treated with generic alendronate as compared to those treated with original once weekly bisphosphonates [30]. Another major concern about these new "Alendronic acids" seems to be also a reduced medication compliance in clinical practice. An additional issue is related to the major disadvantage of the clinically utilized oral bisphosphonates which is their poor oral absorption from the gastrointestinal tract, typically less than 1% is absorbed. The poor absorption of bisphosphonates is most likely due to their very poor lipophilicity and charge, which prevents transcellular transport across the epithelial barriers. The question arises whether the absorption of generic Alendronates, and thus its bioavailability, is further altered because of the variation in galenic/tablet properties. This can potentially affecting the clinical outcome when used in the treatment of osteoporosis. The aim of this retrospective patient chart analysis study was to compare the effects on compliance, persistence, adverse events and on BMD in patients with postmenopausal osteoporosis treated with either different generic Alendronates once weekly or with the original branded compounds Fosamax® (Alendronate) or Actonel® (Risedronate) [21,31-33]. Relevant literature was reviewed.

Patients and study design

In this retrospective patient data analysis we reviewed clinical records of 204 women (50 years of age and older) with postmenopausal osteoporosis for relevant standard patient baseline data and for one year observational treatment results using a standardized patient chart data entry sheet. Patients were eligible from files of our out-patient department for this review if they were above 50 years of age and had initial BMD T-score values lower than –2.5 SD at lumbar spine (LS) and lower than –2.0 SD at the total hip (TH) with or without prevalent vertebral fractures. All participants gave verbal consent to participate in this retrospective patient data analysis. The study was approved by the local Hospital Research Ethics Committee. Selected patients were either without any pre-treatment or with different previous treatments except bisphosphonates (e.g. HRT, raloxifen, tibolone, calcitonin, alfacalcidol, calcium, plain vitamin D). They had started with a once weekly bisphophonate therapy between three or at least one year before this evaluation and were allocated consecutively, according to their treatment to join one of three arms: (A) Generic alendonate 70 mg once a week, (B) Alendronate (Fosamax®) 70 mg once a week and (C) Risedronate (Actonel®) 35

mg once a week. A further selection criterion was initial prescription of 1200 mg calcium and 800 IU Vitamin D per day. BMD DXA-measurements (GE Lunar Prodigy™ DXA Bone Densitometer) and lateral vertebral morphometry (LVA, GE Lunar Prodigy™) or x-rays from thoracic and lumbar spine had to be performed at baseline and after 12 months. Patients of all three groups were excluded if they had been switched to another specific drug therapy (non-bisphosphonates) during the one year of follow-up. Switching to a generic or another branded original bisphosphonate in group B or C during the one year of observation was an exclusion criterion, while in group A switching from one to another generic alendronate was allowed. Not all information about the frequency of switching generic alendronates in group A and on the respective manufactures were available in the patient charts. In table 1 the initial characteristics of the 186 patients are given who fulfilled all above criteria. To assess patients persistence patients were asked using a standardized semi-structured questionnaire during the routine follow-up visit at month 12 how long they remained on therapy (calcium, vitamin D and/or and/or branded or generic bisphosphonate once a week) and when they stopped taking their osteoporosis drug (calcium, vitamin D and/or and/or branded or generic bisphosphonate once a week) for a prolonged period of time. Also during the routine follow-up visit at month 12 patients were asked how they take they drug regimen. Compliance was determined asking the patient how they took their osteoporosis medication and if they took their it on time. Patient´s verbal feedback regarding compliance and persistence was rated and coded in the clinical record.

Statistical methods

186 of the 204 women with postmenopausal osteoporosis who fulfilled the inclusion criteria were included in the retrospective patient data analysis. Baseline characteristics were summarized using descriptive statistics. Formal statistical modeling was performed using SAS Version 9.1. All statistical tests were 2-sided at the 5% level of significance.

Results

Persistence

Table 2 shows the numbers and percentages of patients still on bisphosphonate therapy and on calcium/vitamin D supplementation after 12 months and the average months of intake for the three treatment groups. Still on their respective BP-therapies were 68% of group A (Generic Alendonate 70 mg products), 84% of B (Branded Alendronate (Fosamax®) 70 mg) and 94% of C (Branded Risedronate (Actonel®) 35 mg). The persistence of patients treated with Generic Alendonate 70 mg products was significantly lower as compared to each of the two original branded BP treated groups (Figure 1). In correspondence to these findings the persistence with calcium vitamin D supplementation was also lower in group A than in groups B and C.

Adverse events

During the 12 months of observation gastrointestinal adverse events were documented in 32 patients with Generic Alendonate 70 mg products therapy (group A), 15 with branded Alendronate 70 mg and 9 with branded Risedronate 35 mg once weekly (Table 3). The prevalence of gastrointestinal adverse events was significantly higher in Group A. Other non-gastrointestinal AEs were observed in 14 patients of group A and 9 and 5 resp. in groups B and C (Table 4). Only the difference between generic alendronates and branded Risedronate (Actonel®) 35 mg was statistically significant (Table 4).

Bone mineral density

The average increase in lumbar spine BMD after 12 months amounted to 2.8%, 5.2 and 4.8 for the groups A: Generic Alendonate 70 mg products, B: Branded Alendronate (Fosamax®) 70 mg and C: Branded Risedronate (Actonel®) 35 mg respectively (Figure 2). The respective mean changes at the total hip site were 1.5%, 2.9%, and 3.1%. At both sites the mean increases in BMD were not different between the two groups receiving original branded BP´s (B, C) but for both significantly higher than for group A treated with generic Alendonate 70 mg products (Figure 2).

Discussion

The total number of patients reporting gastrointestinal events were significantly higher in patients treated with generic Alendonate 70 mg once weekly products then with the two branded original bisphosphonates treated patients. Data analysis shows after 12 months significantly higher average BMD increases at lumbar spine and at total hip for patients treated with the branded original bisphosphonates Alendronate (Fosamax®) 70 mg once weekly and Risedronate (Actonel®) 35 mg once weekly compared with generic Alendonate 70 mg once weekly products treated patients. While a significantly higher incidence in gastro-intestinal adverse events with generic alendronates has been published (30), this is the first report demonstrating a significantly lower increase of lumbar spine and total hip bone mineral density after one year with weekly 70 mg treatment with generic alendronate as compared to branded Alendronate (Fosamax®) or Risedronate (Actonel®). As compared to generic Alendronate the average one year increase rates with original Alendronate (Fosamax®) or Risedronate (Actonel®) treatment at the lumbar spine were 86% and 71% higher respectively, and at the proximal femur 93% and 107% respectively (Figure 2). In our study the persistence of patients treated with generic Alendonate 70 mg once weekly products was significantly lower as compared to each of the two with branded original bisphosphonates treated patient groups.

What could be possible explanations for these significant differences in the therapeutic response?

1. Smaller increases in BMD due to lower persistence as a consequence of a higher rate of adverse events?
2. Lower bioavailability and higher rate of adverse events due to differences in disintegration and dissolution properties and esophageal transit time of tablets?
3. Smaller increases in BMD due a false intake of generic alendronate?
4. Smaller increases in BMD due to lower persistence as a consequence of additional psychological factors?
5. A combination of any of the previous 4 ones?

Smaller increases in BMD due to lower persistence as a consequence of a higher rate of adverse events

Since a significantly lower persistence with generic bisphosphonates was shown in our study (Figure 1) this may be indeed the major factor leading to the highly significant lower increases in BMD at both measuring sites. Different studies in recent years proved significant correlations between compliance and therapeutic results during bisphosphonate therapy [26,34,35]. It was shown that noncompliance with antiresorptive therapies has been associated with a 16–50% increased risk of fracture [26,34-38]. Also it was proven that subgroups with good compliance with bisphosphonates (e.g. over 80%) had higher increases in bone mineral density (BMD) and a significantly stronger effect on fracture risk than those with poor compliance [26,27,37].

Lower bioavailability and higher rate of adverse events due to differences in disintegration and dissolution properties and esophageal transit time of tablets

The lower persistence in patients treated with Generic Alendronate 70 mg (and Generic Alendronate 70 mg) once weekly products which was shown in our study could be explained by the higher rates of gastrointestinal adverse events (Table 3). There exists some evidence that branded Risedronate might be a slightly better suitable alternative bisphosphonate drug for gastrointestinal sensitive patients compared to original branded or generic Alendronate [7-9,32,33,39-46]. Two recent studies have shown differences in tablets properties that might explain different rates of adverse events. An in vitro study compared the disintegration and dissolution of once weekly original branded Risedronate (Actonel®) and original branded Alendronate (Fosamax®) tablets with 26 different Generic Alendronate copies from Canada, Germany, the Netherlands and UK [47]. The mean disintegration times of the Generic Alendronate tablets in vitro ranged from 14 to 342 seconds (5.7 min) [47]. The mean disintegration time of the branded product tablets (Actonel® and Fosamax®) ranged only from 43 to 78 seconds [47]. Six of the 26 companies market alendronic acid tablets had very rapid disintegration times which are similar to those of orally disintegrating tablets (non-bisphosphonates) [47]. Since there is no established disintegration time for Alendronate tablets there can be no assurance that the Generic Alendronate copy tablets are equivalent to the branded product in terms of esophageal drug exposure [47].

Another trial evaluated and compared esophageal transit times and in vivo disintegration of one branded risedronate and two generic formulations of alendronic acid tablets [48], that are

commercially available in Canada and the United Kingdom. It was shown, that the two generic formulations of alendronic acid tablets had significant slower transit times than compared with the branded risedronate (Actonel®) tablet tested [48]. The branded risedronate tablet had a significantly faster transit time than the two generic formulations of alendronate tested [48]. This is of importance for patients because delayed esophageal transit or disintegration of oral bisphosphonate tablets before they enter the stomach could cause iatrogenic complications. Different formulations of generic bisphosphonate tablets meeting regulatory requirements may have substantial differences in pharmaceutical attributes from the branded product that may result in different characteristics during esophageal transit. A potential concern is that the pharmaceutical attributes of the various copy alendronate formulations may affect the potential for local irritation and tolerability, especially in the upper gastrointestinal tract. Epstein and colleagues [49] showed a greater irritant response from a copy Alendronate tablet (Novo-Alendronate† 10 mg) in a rabbit injection study and in a dog esophageal study (Alendronate Sodium Tablets, Teva Industries, Petah-Tikva, Israel) compared to the branded innovator product (Alendronate sodium tablets, 10 mg). The differences were attributed to the pharmaceutical preparation, since the active ingredient (Alendronate sodium) and the dose were similar between the copy Alendronate tablets and the branded tablets. The same authors (50) also evaluated the disintegration and dissolution profiles of 13 copy Alendronate tablets available in Latin America. From a safety perspective, the authors concluded that for the rapidly disintegrating formulations there is a chance that disintegration may occur in the mouth and/or the esophagus during swallowing of the tablet. This could increase the duration and extent of oral and esophageal tissue exposed to semi-particulate alendronate and thereby increase the risk of serious mucosal irritation and ulceration [50]. From an efficacy perspective, Epstein et al. also concluded that tablets that disintegrate faster than branded Alendronate sodium tablets (1.4 min) could result in reduced efficacy because the premature disintegration may be associated with semi-particulate Alendronate being retained within the esophagus, increasing the likelihood of contact with ingested food, saliva, mucus or liquids, thereby reducing the bioavailability or altering the pharmacokinetics. The bioavailability and therefore the efficacy of some generic Alendronate products due to very short disintegration times of the tablets (and a significant slower esophageal transit time of Generic

Alendronate tablets) could be reduced. Generic Alendronate tablets with very short disintegration times start to disintegrate very quickly already in the mouth and esophagus. The already low intestinal absorption rates of these generic bisphosphonate drugs could be further decreased and full efficacy in terms of BMD increases not reached. The difference in the gastrointestinal safety and tolerability profile in favour for Risedronate vs Alendronate could together with the inferior disintegration and dissolution characteristics and significant slower esophageal transit time of once weekly generic Alendronate tablets explain the higher rates of gastrointestinal adverse events and lower efficacy detected in patients treated with Generic Alendronate in our study. Higher rates of gastrointestinal adverse events could have implications on persistence for patients which could lead to smaller increases in BMD. All together the described inferior gastrointestinal safety and tolerability profile of Alendronate compared to Risedronate would become even worse due to differences in disintegration and dissolution properties and a significant slower esophageal transit time of Generic Alendronate tablets. This could due to the higher rates of gastrointestinal adverse events (Table 3) and lower bioavailability have implications on persistence and on efficacy for patients which could lead to smaller increases in BMD.

Smaller increases in BMD due a false intake of generic Alendronate

A prerequisite of good therapeutic results in osteoporosis with the oral N-BP´s like Risedronate or Alendronate is the correct intake. Bioavailability of oral bisphosphonates is poor due to low intestinal absorption rates [51]. The correct intake of a poorly absorbed bisphosphonate tablet is even more important if it is only given once per week. Food, calcium and other polyvalent cations can further decrease the absorption of these drugs, due to complex formation [52]. To ensure unimpaired intestinal absorption, correct intake of the bisphosphonate on an empty stomach in upright position early in the morning with a glass of tap water and avoidance of any other beverage, food or medicines at least 1/2 an hour thereafter is required for Risedronate and Alendronate. Non-compliance with these instructions may lead to a lower absorption of the bisphosphonate with a risk of impaired treatment outcome. The risk of mistakes and reduced

compliance when treating osteoporosis with a weekly oral bisphosphonate may be enlarged by frequent changes of prescribed or dispended bisphosphonates often without physicians not having the time to explain the reasons appropriately. Frequent changes of prescribed or dispended bisphosphonates especially generic Alendronate tablets and packages could lead to a complexity of therapy and a less good understanding of the regimen and thereby decrease the chance of a correct and effective medication. Therefore the likelihood to meet therapeutic goals of the therapy can be decreased.

Smaller increases in BMD due to lower persistence as a consequence of additional psychological factors

There could exist other additional factors that may explain differences in compliance and persistence and therefore efficacy. It cannot be excluded that besides adverse events psychological factors may contribute to a reduced persistence with generic alendronates. The knowledge about being treated with generics may have an influence on patients behaviour. The perception of receiving a cheap or "second choice" medication may considerably reduce the acceptance and compliance in individual patients. Also in the above cited Canadian study looking for gastrointestinal adverse events after switching from branded Alendronate to generic Alendronate there were significantly more adverse events during the second treatment phase although the patients were unaware of having been switched to generics [30].

Study limitations

The present retrospective single centre-study under practical real life conditions has a few limitations mainly due to the way data have been collected. As with all observational studies, systematic errors (e.g. selection bias) may be the basis for the observed results [53]. On the other hand in our study there were no statistical differences in measurable patients characteristics between the 3 cohorts of patients at initiation of therapy. Strengths of this study include that all

interviews regarding compliance and persistence were conducted by one interviewer using a standardized semi-structured questionnaire designed to analyze a clearly study outcome. However, this design has limitations. As a survey, it evaluates a patient's level of present understanding of the dosing instructions, compliance and persistence but cannot truly represent the respondent's previous behaviour in taking the medication. Given that the long-term treatment goal is to improve adherence with bisphosphonates, randomization of women to either branded or Generic bisphosphonates with assessment of adherence would be an improved design for future clinical prospective studies. The strength of observational studies can be the generalizability of results. In contrast, the generalizability of results from randomized trials to a real world setting can be limited by differences between the two in relation to expertise of health care provider, quality of medical care, course of therapy, and types of patients [54]. For example, it has been observed that the majority of patients considered candidates for osteoporosis therapy by their physician would not meet the eligibility criteria for inclusion in the randomized trials [55].

Summary and conclusions

Significantly lower increases of lumbar spine and total hip BMD with generic alendronate once weekly as compared to the two branded originals (Fosamax®, Actonel®) were observed. The reasons for the 40-50% lower BMD increase rates when using the generic compounds are not know yet. At least in part the lower efficacy can be explained by a significantly lower degree of persistence with generic alendronate, which could be related to a higher incidence of gastrointestinal adverse events. Other reasons could be lower bioavailability or potency of generic alendronate. We conclude from our study results that in daily practice there may be a high risk of a relatively reduced compliance with generic alendronate as compared to the original branded once weekly bisphosphonate tablets. This may considerably impair therapeutic outcomes and from a health economic point of view the lower price of generic alendronate will be no longer an advantage. Further studies to prove the possible risk of a reduced therapeutic effectiveness when prescribing generic alendronate are urgently needed.

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Figures:

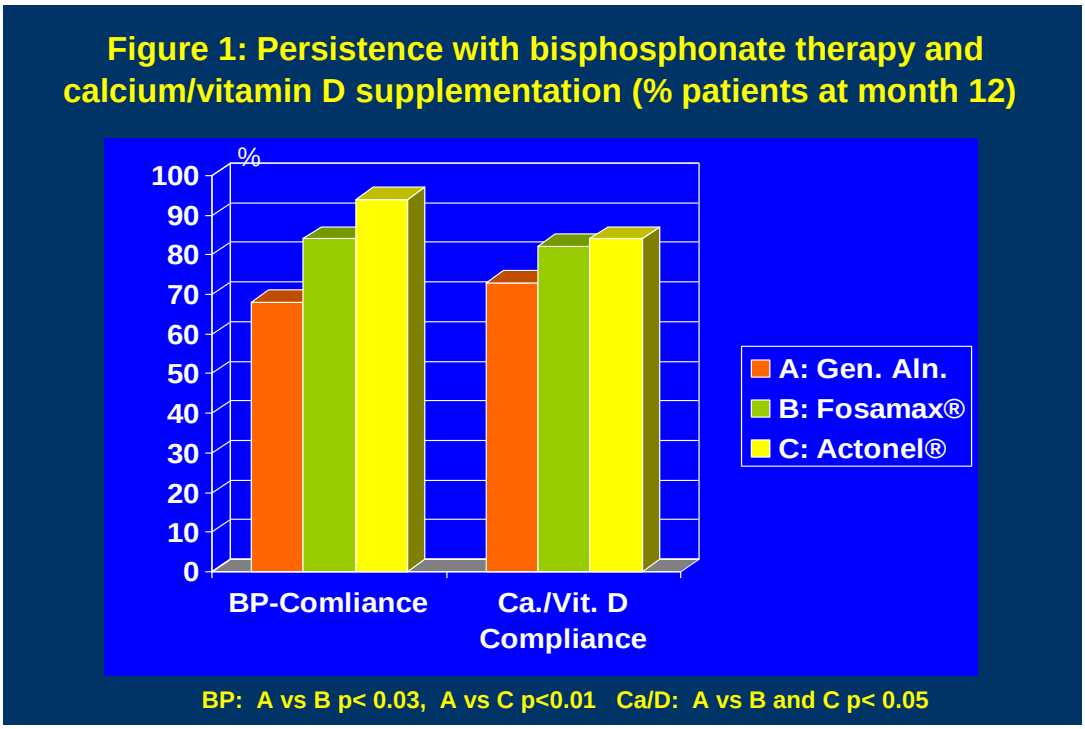
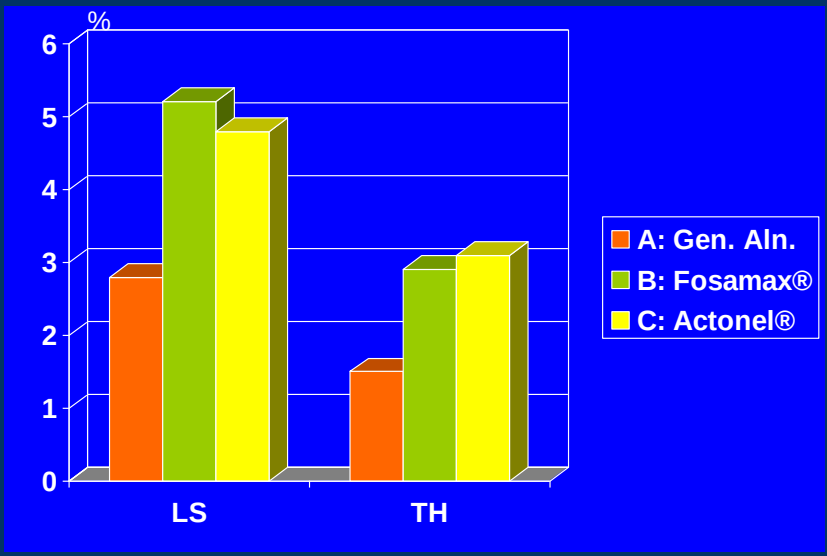


Figure 2: Mean percent changes in lumbar spine (LS) and total hip (TH) BMD after 12 months



LS: A vs B and C p< 0.05 TH: A vs B and C p< 0.01

Tables:

Table 1: Baseline characteristics of patients*

	Gen. Aln.	Fosamax®	Actonel®
Number of patients (n)	62	62	62
Mean age (years)	63.7	64.2	65.8
Mean height (cm)	165.5	164.0	162.5
Mean weight (kg)	70.2	69.6	68.5
LS-BMD (T-Score)	-3.05	-3.11	-3.16
TH-BMD (T-Score)	-2.91	-2.81	-2.87
Pat. with preval. vert. fractures (n)	35	38	41
Pat. with preval. vert. fractures (%)	56%	61%	66%
Pat. with preval. non-vert-fractures (n)	17	19	20
Pat. with preval. non-vert-fractures (%)	27%	31%	32%

*No signif. diff. between groups

Table 2: Persistence with bisphosphonate therapy and calcium/vitamin D supplementation at month 12

	Gen. Aln. (n=62)	Fosamax® (n=62)	Actonel® (n=62)
Pat. still on BP (n)	40	52	58
at month 12 (%)	68%	84%	94%
Mean duration of (m) intake of BP*	9.5	11.0	11.6
Pat. still on Ca/D (n)	43	51	52
at month 12 (%)	73%	82%	84%
Mean duration of (m) Intake of Ca/D	8.8	10.2	10.7

*All patients (ITT-Population)

Table 3: Number of patients with gastrointestinal adverse events during the 12 months follow-up period

	Gen. Aln. (n=62)	Fosamax® (n=62)	Actonel® (n=62)
Mild epigastric discomfort	4	2	1
Epigastric pain	7	2	3
Esophageal burning	5	3	0
Nausea	5	2	1
Vomiting	2	0	0
Diarhea	3	1	1
Obstipation	2	3	2
Meteorism	4	2	1
All GI adverse events	**32***	**15**	**9**

*vs Fosamax p<0.05, vs Actonel p<0.01, Fos.vs Act. ns

Table 4: Number of patients with non-gastrointestinal adverse events* during the 12 months follow-up period

*Vert. and non-vert Fx were captured as AE (i.e. clinical Fx)

	Gen. Aln. (n=62)	Fosamax® (n=62)	Actonel® (n=62)
Arthralgia	2	2	1
Bone pain	1	1	0
Muscle cramps	2	1	0
Headache	2	0	1
Dizziness	1	1	0
Vertebral Fx	4	3	2
Non-vert. Fx	2	1	1
All other AE*	**14**	**9**	**5**

***A vs B ns, B vs C ns, A vs C p< 0.05**