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Full Length Research Paper

Efficacy of different medicines used for the treatment of osteoporosis by using dual energy x-ray absorptiometry

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Osteoporosis, a skeletal disease and common condition affecting one in three women and one in twelve men is a major health burden worldwide and in our population as well. A total of 180 patients including 30 in control group, 126 osteoporotics and 54 osteopenics, were diagnosed and analyzed with the help of bone mineral density (BMD) by dual energy x-ray absorptiometry (DEXA) and treated in different groups with different brands of medicines; bisphophonates (alendronates and risederonates). Overall results in the therapy group BMD (g/cm²) spine improved from 0.748 ± 0.0088 to 0.777 ± 0.0091 after one year of treatment while BMD hip rose from 0.713 ± 0.0087 to 0.730 ± 0.009 in a similar period. In the osteoporotic group (n = 106), BMD spine increased from 0.699 ± 0.0077 to 0.727 ± 0.007 and BMD hip from 0.679 ± 0.009 to 0.693 ± 0.009. In the osteopenic goup (n = 44), BMD spine increased from 0.863 ± 0.011 to 0.898 ± 0.011 and BMD hip from 0.793 ± 0.007 to 0.817 ± 0.012. Patients on Osto, Drate and Fosamax (alendronates) did better than those on Dronate and Actonel (risedronates). Of alendronates, Fosamax and Osto treated patients did better than those on Drate. Of risedronates, Actonel treated patients faired better than those on Dronate which showed the least improvement.

Key words: Osteoporosis, osteopenia, bone mineral density, DEXA, alendronate, risedronate.

INTRODUCTION

Osteoporosis is a skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk. Osteoporosis is a common condition affecting one in three women and one in 12 men, resulting in a substantial morbidity, excess mortality, health and social services expenditure (Nelson et al., 2002). The WHO definition of osteoporosis is based on measurement of bone mineral density (BMD) of >2.5 standard deviations (SD) below the mean for young adults, while osteopenia is defined as a BMD between 1 and 2.5 SDs below the means for young adults (T score) (Estell, 1998) (WHO report, 1994). The risk of fracture increases to three fold for each SD decrease in BMD (Martial et al., 1996). The disease is common in post-menopausal women (Melton et al., 1990); however, the disease prevalence varies in different population. Umer et al. (2003) reported the prevalence of osteoporosis 8.7% and osteopenia 22.5% in postmenopausal in Mayo hospital Lahore. In another mega study, 40% postmenopausal osteopenia and 7% osteoporosis was found by peripheral bone densitometry (Siris et al., 2001). It is widely accepted that BMD measurement using DEXA is the gold standard of diagnosis for osteoporosis (Siris et al., 2001; Lewiecki et al., 2004; Grampp et al., 1999). A study conducted by Habiba et al. (2002) at Hayatabad

Medical Complex, Peshawar in 1997 to 1998 on thousand postmenopausal women for simple calculated osteoporosis risk estimation, found that 75.3% were predisposed to osteoporosis and the risk increased with age (97% in women of 75 to 84 years of age compared to 55% in women of 45 to 54 years of age). The importance of developing treatments that reduce the risk of fracture is evident, both from an individual and a societal perspective, and a number of agents are available that have been shown in randomized controlled trials to decrease the risk of vertebral and, in some instances, non-vertebral fracture (Delmas, 2002; Compston et al., 2009). Major pharmacological interventions are the bisphosphonates, strontium ranelate, raloxifene, deno-sumab and parathyroid hormone peptides. They are approved only for the treatment of postmenopausal osteoporosis, but alendronate, etidronate, risedronate and zoledronic acid are also approved for the prevention and treatment of glucocorticoid-induced osteoporosis (Van Staa, 2006; Compston, 2007) and alendronate, risedronate, zoledronate and teriparatide are approved for the treatment of osteoporosis in men (Papaioannou et al., 2010; Compston et al., 2009).

The alendronate is USFDA approved for the prevention and treatment of osteoporosis in postmenopausal women. It is also approved as a treatment to increase bone mass in men with osteoporosis and glucocorticoid induced osteoporosis in both men and women.

Alendronate prevents osteoporosis in post-menopausal women (McClung et al., 1998). Alendronate reduces new vertebral and non-vertebral fractures during treatment of osteoporosis (Black et al., 1996). The effects of alendronate in osteoporotic men appear similar to those seen in postmenopausal women (Orwoll et al., 2000). There is significant change in BMD in patients using long term prednisolone therapy (Saag et al., 1998). The 5 mg daily dose and 35 mg weekly dose have been approved by the FDA for prevention of postmenopausal osteoporosis, and the 10 mg daily dose and 70 mg weekly dose have been approved for treatment in men and postmenopausal women (Peters et al., 2001).

Risedronate was recently approved for treatment of osteoporosis. The results appear similar to alendronate. Risedronate significantly reduces the risk of hip fracture among elderly women with confirmed osteoporosis but not among elderly women selected primarily on the basis of risk factors other than low bone mineral density. There are conflicting data about whether more gastrointestinal side effects are seen with alendronate than with risedronate. At this time, this newer bisphosphonate does not seem to provide any definite advantage to alendronate for the treatment of osteoporosis, other than possibly price. Risedronate prevents osteoporosis in post-menopausal women (Hooper et al., 1999; Fogelman et al., 2000). Alendronate reduces new vertebral and non-vertebral fractures during treatment of osteoporosis (Reginster et al., 2000; Harris et al., 1999). There is significant change in BMD in patients using long term prednisone therapy (Cohen et al., 1999; Reid et al., 2000). For treatment in postmenopausal women and for treatment in perimenopausal women (35 mg tablet once a week or 5 mg tablet once daily). For treatment and prevention in men and women 5 mg tablet once daily. It has been demonstrated in studies to increase bone mass in the spine and hip and reduce the risk of spine and non-spine fractures by 40 to 50% over a 3 to 5 year period. 30 mg is given once daily for 2 months. It is a USFDA approved drug for treatment of Paget's disease (Peters et al., 2001).

According to our knowledge, not much work has been done so far on osteoporosis in particular on efficacy of different medicines and BMD. The objective of the study was to find out the efficacy of different medicines with the help of bone mineral density (BMD) measured by latest technique of dual energy X-ray absorptiometery (DEXA) for the diagnosis and treatment of osteoporosis in pre and postmenopausal women of Karachi.

MATERIALS AND METHODS

Setting

The study was conducted for a period of two years and each patient studied (treated and analyzed) for one year in patients attending the outpatient department of Karachi Institute of Radiotherapy and Nuclear Medicine, Karachi.

Sample size and characteristics

This study was carried out on 180 postmenopausal women, belonging to the urban population of Karachi. Out of those, 30 subjects were placed in the control or placebo group while 150 patients of osteoporosis/osteopenia underwent therapy. Patients undergoing therapy were further subdivided into five sub-groups of 30 each; depending on the drug treatment they received, that is, Osto, Drate, Fosamax, Dronate or Actonel.

On the basis of BMD values, patients were diagnosed as having osteoporosis or osteopenia and their data was calculated on a quarterly basis. The "term baseline" or "0 month" refers to the time when patients were initially admitted and treatment initiated. Similarly 3, 6, 9 and 12 months refer to the length of time of treatment from baseline or 0 month.

Patient selection

After considering the detailed history taken from patients, the population is selected for the study in which no family history of osteoporosis, thyroid disorder and other factors observed which may affect the bone mineral density.

Detailed history from the patient was taken concerning previous drug, surgical, medical, gynaecological history, and if any test has been performed previously. The detailed performance was also filled by the patient.

Design

Bisphosphonates (Alendronate and Risedronate) were prescribed to the patients under different brand names according to the indicated dosage. The primary end point was the change in bone

mineral density at the hip and spine. Bone mineral density was measured quarterly (0, 3. 6, 9 and 12 months) by dual-energy x-ray absorptiometry in a blinded fashion.

Dosage

The usual dosing recommendations are according to Peters et al. (2001). In our study, the dosage was:

1. Alendronate
(a) FOSAMAX 70 mg weekly
(b) DRATE 70 mg weekly
(c) OSTO 70 mg daily

2. Risedronate
(a) DRONATE 35 mg weekly
(b) ACTONEL 35 mg weekly

The drug is to be taken only upon rising for the day with three swallows of water, not to exceed 6 to 8 oz. Stand, walk or sit and remain fasting for 30 to 45 min afterwards, then take breakfast. Lying down or reclining prior to taking breakfast may cause gastroesophageal reflux and esophageal irritation. At least 30 min should be allowed to pass before meals or other beverages than water is taken in.

i) Alendronate and risedronate are generally well tolerated as long as they are taken appropriately to avoid upper gastrointestinal adverse effects.
ii) Alendronate is slightly more expensive than risedronate; however, the once-weekly form of alendronate may enhance patient compliance and tolerability enough to offset the higher cost.
iii) Alendronate is not FDA-approved for preventing glucocorticoid induced osteoporosis.

Side effects

1. GI tract: A severe side effect is an ulceration of the esophagus caused by alendronate, which may require hospitalization and intensive treatment. Gastric and duodenal ulceration.
2. General: Infrequent cases of skin rash, rarely manifesting as Stevens-Johnson syndrome and toxic epidermal necrolysis, eye problems (uveitis, scleritis) and generalized muscle, joint, and bone pain (rarely severe) have been seen. In laboratory tests, decreased calcium and phosphate values may be obtained but reflect action of the drug and are harmless.
3. Cases of osteonecrosis of the jaw have been reported in the medical literature, but relationship to alendronate is unknown.
4. Osteonecrosis of the jaw-deterioration of the TM joint can also result specially in cancer patients.
5. Rare instances of auditory hallucinations and visual disturbances have been associated with alendronate and other bisphosphonates.

DEXA

Bone mineral density was measured by latest technique of DEXA. BMD was measured by DXA with a QDR (quantitative digital radiography) discovery device (Hologic, Waltham, MA, USA) at the lumber spine (LS BMD) and total hip (H BMD) at KIRAN, Karachi.

Statistical analysis

Statistical analysis of this study was carried out using, SPSS for windows version 12.0 and MedCalc® version 9.5.2.0. Variables for SPSS were defined according to the parameters listed in patient data form. Data was entered with sequence represent in patient data form for each treatment group and finally of control group. Least significant change of the system was calculated using spine phantom. By taking LSC = 2% for both Hip and Spine ROC, curves were obtained using MedCalc® version 9.5.2.0. Corresponding cut-offs and positive predictive values (PPV), negative predictive values (NPV), sensitivity and specificity were also calculated at 3, 6, 9 and 12 months of overall population (except control group). Correlation is significant at the 0.01 level (2-tailed). All aforementioned parameters were also calculated on treatment group basis.

RESULTS

Table 1 shows the characteristics of the population of this study. Table 2 shows the comparison of biophysical parameters of the therapy and control groups.

In the therapy group, BMD (g/cm²) spine improved from 0.748 ± 0.0088 to 0.777 ± 0.0091 after one year of treatment while BMD hip rose from 0.713 ± 0.0087 to 0.730 ± 0.009 in a similar period (Table 3). The values are expressed as mean ± standard error (SE) in mean. Table 3 shows the average BMD spine and BMD hip of all the patients (n = 150) in the therapy group at baseline and at 3, 6, 9 and 12 months. The values are expressed as mean ± standard error (SE) in mean

In the osteoporotic group (n = 106), BMD spine increased from 0.699 ± 0.0077 to 0.727 ± 0.007 and BMD hip from 0.679 ± 0.009 to 0.693 ± 0.009. In the osteopenic group (n = 44), BMD spine increased from 0.863 ± 0.011 to 0.898 ± 0.011 and BMD hip from 0.793 ± 0.007 to 0.817 ± 0.012 (Table 4). The values are expressed as mean ± standard error (SE) in mean. In Table 4, data of BMD spine and hip is given based on the sub-classification of patients into osteoporosis (n = 106) and osteopenia (n = 44) groups.

The five therapy sub-groups behaved much differently than the control group. In the control group, BMD fell from 0.757 ± 0.014 to 0.741 ± 0.014 in case of spine and from 0.729 ± 0.017 to 0.719 ± 0.017 in case of hip, over a one year period (Table 5). In Table 5 data of BMD spine in therapy and control groups against treatment time is shown. The values are expressed as mean ± standard error (SE) in mean.

In case of Osto, Drate, Actonel and Fosmax, it rose steadily for spine (0.786 ± 0.023 to 0.827 ± 0.025, 0.734 ± 0.017 to 0.764 ± 0.018, 0.736 ± 0.017 to 0.763 ± 0.015, and 0.739 ± 0.019 to 0.774 ± 0.020, respectively) (Table 5) and hip (0.734 ± 0.023 to 0.761 ± 0.024, 0.715 ± 0.021 to 0.730 ± 0.022, 0.692 ± 0.015 to 0.708 ± 0.015 and 0.722 ± 0.019 to 0.746 ± 0.02, respectively) (Table 6).

However, a somewhat different pattern was noted in case of Dronate) (Tables 5 and 6). In Table 6 data of BMD hip in therapy and control groups against treatment time is shown. The values are expressed as mean ± standard error (SE) in mean.

After an initial rise till six months, a subsequent drop was noted. It can be appreciated that the average BMD in osteoporosis group is less than that in osteopenia group because of greater bone loss in former.

Table 1. Comparison of biophysical parameters of therapy and control groups.

Parameter	Therapy group	Control group
Total no of subjects	150	30
Patients with osteoporosis	106	20
Patients with osteopenia	44	10
Mean age (years)	55.10	55.60
Age range (years)	37-76	46-69
Mean Weight (kg)	60.86	61.26
Weight range (kg)	35-85	39-76
Average time since menopause in osteoporosis group (years)	10.67	8.15
Average time since menopause in osteopenia group (years)	8.50	9.40

Table 2. Demographic data of sub-groups of the study population.

Group	Osteoporosis			Osteopenia		
	Mean age (years)	Mean height (cm)	Mean weight (kg)	Mean age (years)	Mean height (cm)	Mean weight (kg)
Osto	56±8	55±10	149±3	53±7	68±7	153±3
Drate	56±6	57±8	150±4	54±11	65±7	158 ± 11
Dronate	56±6	58±10	150±7	49±10	66±10	150±7
Actonel	53±7	57±7	152±7	55±9	65±8	154±5
Fosamex	57±7	58±10	152±6	54±7	74±5	156±4
Control	55±5	58±8	150±6	55±5	66±6	151±7
Total	55±6	57±9	151±5	53±8	68±7	153±6

Table 3. Average BMD of spine and hip of all patients in the therapy group (improvement of spine and hip BMD with therapy)

Time (months)	BMD spine	BMD hip
0	0.748 ± 0.0088	0.713 ± 0.0087
3	0.763 ± 0.0087	0.717 ± 0.0088
6	0.768 ± 0.0089	0.723 ± 0.0087
9	0.772 ± 0.0090	0.726 ± 0.0088
12	0.777 ± 0.0091	0.730 ± 0.009

Table 4. Comparison of BMD spine and hip in osteoporotic and osteopenic patients after treatment.

Time (months)	BMD spine		BMD hip	
	Osteoporosis (n = 106)	Osteopenia (n = 44)	Osteoporosis (n = 106)	Osteopenia (n = 44)
0	0.699 ± 0.0077	0.863 ± 0.011	0.679 ± 0.009	0.793 ± 0.0077
3	0.717 ± 0.008	0.873 ± 0.011	0.683 ± 0.009	0.799 ± 0.008
6	0.720 ± 0.008	0.883 ± 0.011	0.689 ± 0.009	0.804 ± 0.008
9	0.723 ± 0.008	0.889 ± 0.011	0.691 ± 0.009	0.810 ± 0.008
12	0.727 ± 0.007	0.898 ± 0.011	0.693 ± 0.009	0.817 ± 0.012

In terms of percentage change in BMD after one year, the groups behaved variably. Osto treated patients showed an improvement in BMD of 5.21% for spine and 3.67% for hip at 12 months. In case of Drate, it was 4.08% for spine and 2.11% for hip. For Actonel, it was 3.66% for spine and 2.31% for hip. In case of Fosamax,

Table 5. BMD spine in therapy and control groups against treatment time.

Time (months)	Osto	Drate	Dronate	Actonel	Fosamax	Control
0	0.786 ± 0.023	0.734 ± 0.017	0.743 ± 0.022	0.736 ± 0.017	0.739 ± 0.019	0.757 ± 0.014
3	0.799 ± 0.023	0.752 ± 0.017	0.762 ± 0.021	0.751 ± 0.016	0.752 ± 0.018	0.753 ± 0.014
6	0.810 ± 0.024	0.756 ± 0.018	0.762 ± 0.021	0.756 ± 0.016	0.759 ± 0.019	0.749 ± 0.014
9	0.818 ± 0.025	0.760 ± 0.018	0.757 ± 0.021	0.758 ± 0.015	0.766 ± 0.019	0.745 ± 0.014
12	0.827 ± 0.025	0.764 ± 0.018	0.755 ± 0.021	0.763 ± 0.015	0.774 ± 0.020	0.741 ± 0.014

Table 6. BMD hip in therapy and control groups against treatment time.

Time (months)	Osto	Drate	Dronate	Actonel	Fosamax	Control
0	0.734 ± 0.023	0.715 ± 0.021	0.699 ± 0.017	0.692 ± 0.015	0.722 ± 0.019	0.729 ± 0.017
3	0.742 ± 0.023	0.716 ± 0.020	0.704 ± 0.017	0.696 ± 0.015	0.728 ± 0.019	0.726 ± 0.017
6	0.746 ± 0.023	0.722 ± 0.021	0.707 ± 0.0170	0.701 ± 0.015	0.739 ± 0.019	0.724 ± 0.017
9	0.751 ± 0.023	0.726 ± 0.021	0.705 ± 0.017	0.704 ± 0.015	0.744 ± 0.02	0.721 ± 0.017
12	0.761 ± 0.024	0.7301 ± 0.022	0.703 ± 0.017	0.708 ± 0.015	0.746 ± 0.02	0.719 ± 0.017

Table 7. Percentage change in BMD spine in therapy and control groups.

Time (months)	Percentage change in BMD spine from baseline (%)					
	Osto	Drate	Dronate	Actonel	Fosamax	Control
3	1.65	2.45	2.55	2.03	1.75	-0.52
6	3.05	2.99	2.55	2.71	2.70	-1.05
9	4.07	3.54	1.88	2.98	3.65	-1.58
12	5.21	4.08	1.61	3.66	4.73	-2.11

Table 8. Percentage change in BMD hip in therapy and control groups.

Time (months)	Percent change in BMD Hip from baseline					
	Osto	Drate	Dronate	Actonel	Fosamax	Control
3	1.089	0.13	0.71	0.57	0.83	-0.41
6	1.63	0.97	1.14	1.30	2.35	-0.68
9	2.31	1.53	0.85	1.73	3.04	-1.09
12	3.67	2.11	0.57	2.31	3.32	-1.37

spine showed 4.73% while hip showed 3.32% improvement at one year. In case of Dronate, spine improved by 2.55% at six months but at 12 months it fell to 1.61%; for hip, it increased by 1.14% at 6 months to drop to only a 0.57% increment at 12 months (Tables 7 and 8).

Patients on Osto, Drate, Fosamax (alendronates) did better than those on Dronate and Actonel (risedronates). Of alendronates, Fosamax and Osto treated patients did better than those on Drate. Of risedronates, Actonel treated patients faired better than those on Dronate which showed the least improvement.

In order to get a better understanding about the improvement in BMD, spine and hip in the five therapy subgroups, the percentage change from baseline was calculated and is given in Tables 7 and 8, and show how the percentage change in BMD spine and hip vary for therapy and control groups. In the group of untreated patients (control), BMD continuously drops so percentage change lies in negative region. Response in case of Osto and Fosamax is quite good throughout the treatment time while it is somewhat slower in case of Drate after 6 months. Much slower improvement is observed in case of Actonel. In case of Dronate, a rise at 3 months and then a continuous drop is observed throughout the treatment course (Tables 7 and 8).

DISCUSSIONS

The increasing awareness of osteoporosis and the development of treatments with proven efficacy are likely to increase the demand for management and monitoring of patients with osteoporosis. This in turn will require widespread facilities for its diagnosis and assessment. Measurements of bone mineral density are a central component since this forms an integral component of the definition of osteoporosis. The internationally agreed description of osteoporosis is 'a systematic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures'. The definition captures the notion that low bone mineral density is an important component of the risk of fracture, but recognizes that other abnormalities in the skeleton contribute to skeletal fragility.

Although the measurement of BMD by DEXA is accepted as the 'gold standard' for establishing the diagnosis of and for follow-up of patients with osteoporosis/osteopenia, it must be emphasized here that sources of potential limitations in the accuracy of the technique must be kept in mind. These may accrue from systematic inaccuracies, biological variability, variable soft tissue densities, site related inaccuracies etc. This highlights the need to establish the performance characteristic of any technique for any site by establishing its sensitivity, specificity, and positive predictive value (Hui, 1988).

The importance of developing treatments against osteoporosis and osteopenia is evident, both from an individual and a societal perspective, and a number of agents are available that have been shown in randomized controlled trials to decrease the risk of vertebral and, in some instances, non-vertebral fracture (Delmas, 2002; Compston, 2009).

Major pharmacological interventions are the bisphosphonates, strontium ranelate, raloxifene, denosumab and parathyroid hormone peptides. Interventions that are approved for the prevention and treatment of osteoporosis in Europe are approved only for the treatment of postmenopausal osteoporosis, but alendronate, etidronate, risedronate and zoledronic acid are also approved for the prevention and treatment of glucocorticoid-induced osteoporosis (Van Staa, 2006; Compston, 2007) and alendronate, risedronate, zoledronate and teriparatide are approved for the treatment of osteoporosis in men (Compston, 2009; Papaioannou, 2010).

A total of 180 patients were included in this study. Out of these, 150 underwent therapy while 30 did not take medication for various reasons like alternate treatment by homeopaths, hakims, diet treatment or other reasons for non-compliance and served as the control group for the study. Patients were sub-classified on the basis of BMD measurements by DXA into osteoporotic (T score < -2.5 SD at any site) and osteopenic (T score between -1.5 to -2.5 SD at any site) groups. Of the 150 patients undergoing therapy (mean age 55.10 years, mean weight 60.86 kg), 106 patients belonged to the osteoporotic group while 44 belonged to the osteopenic group. In the control group (30 patients), 20 were osteporotic while 10 were osteopenic. The therapy group was further sub-divided into 5 groups of 30 patients each depending on the drug treatment given, that is, Osto, Drate, Fosamax (alendronates) or Dronate and Actonel (risedronates).

Data analysis shows after 12 months significantly higher average BMD increases at lumber spine and at total hip for patients treated either with alendronates or risedronates, although five therapy sub groups behaved much differently than the control group.

Although our results contrast with findings from other observational studies that document risedronate as more effective than alendronate in preventing nonvertebral fractures (Watts, 2004; Silverman, 2007), it is also somewhat surprising because randomized, controlled trials (RCTs) show that alendronate improves bone mineral density and reduces bone turnover markers better than risedronate (Rosen, 2005; Bonnick, 2006). Previous studies comparing bisphosphonates included preventive doses of alendronate that are less effective than treatment doses (Cranney, 2002**)**. These differences in study may partially explain the differences between our findings between bisphosphonates, compared with previous studies suggesting that risedronate is more effective than alendronate.

To our knowledge, FACT (Fosamax Actonel Comparison Trial) is the only head-to-head trial comparing alendronate and risedronate (Rosen, 2005; Bonnick, 2006) randomly assigning 1053 postmenopausal women (mean age, 64.5 years) with low bone mineral density to receive weekly alendronate or risedronate, FACT controlled for both measured and unmeasured confounding. However, FACT also excluded important candidate groups for pharmacotherapy with bisphosphonates, such as men, and women with previous hormone or long-term glucocorticoid therapy. Randomized, controlled trials establish drug efficacy within defined patient populations that are often not representative of those who may benefit from pharmacotherapy or of how the agents are used in practice (for example, adherence to drug regimen, and calcium or vitamin D supplementation) (Lindsay, 2007). In contrast, health care claims data reflect routine practice for large and representative populations (Schneeweiss, 2005)**.** Therefore, observational studies play an important role in examining drug effectiveness among those treated. Although alendronate and risedronate recipients in our study were similar according to measured covariates, we cannot rule out possible differences due to unmeasured variables, such as bone mineral density, risk for falls, family history, or nonprescription preventive therapies.

The efficacy of bisphosphonates in reducing

nonvertebral fracture risk is established among persons with a bone mineral density T-score less than −2.5. However, the National Osteoporosis Foundation recommends that treatment be considered at a T-score less than −2.0, and in the presence of other risk factors, at a T-score less than −1.5 (National Osteoporosis Foundation, 2003). It is therefore possible that a high proportion of recipients have a bone mineral density higher than that for which bisphosphonates are documented to be effective. These analyses suggested that our findings are unlikely to be entirely due to unmeasured confounding. Bone mineral density is the most important risk factor for fracture that was not included in our analysis. The relative risk for hip fracture is estimated to be 2.5 at age 65 years among persons with osteoporosis (T-score < –2.5) compared with those with higher bone mineral density (Black, 2006).

The study cohort was limited to low-income families with complete drug coverage residing in Karachi. Thus, our results may not be generalizable to all recipients of these agents, particularly if adherence to treatment differs among those with different drug coverage. However, our cohort of frail persons age 65 years or older is typical of patients requiring pharmacotherapy to reduce fracture risk and provides real-world comparative effectiveness data among patients with complete drug coverage.

In the absence of RCT evidence, observational data provide a complementary source of information that compares drug effectiveness when prescribed in clinical practice (Lindsay, 2007). Our large observational study of persons age 65 years or older who received drug treatment for osteoporosis, identified no difference in the effectiveness of bisphosphonates (risedronate versus alendronate) in preventing nonvertebral fractures. We also documented no large differences in fracture risk among raloxifene compared with alendronate. However, confidence bounds were wide and thus do not rule out potentially important clinical differences.

REFERENCES

Black DM, Cummings SR, Karpf DB (1996). Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet, 348:1535-1541.

Black DM, Palermo L, Grima DT (2006). Developing better economic models of osteoporosis: considerations for the calculation of the relative risk of fracture. Value Health, 1: 54-8.

Bonnick S, Saag KG, Kiel DP, McClung M, Hochberg M, Burnett SM (2006). Comparison of weekly treatment of postmenopausal osteoporosis with alendronate versus risedronate over two years. J . Clin. Endocrinol. Metab., 91: 2631-2637.

Cohen S, Levy RM, Keller M (1999). Risedronate therapy prevents corticosteroid- induced bone loss: a 12-month, multicenter, randomized double-blind, placebo-controlled, parallel-group study. Arthritis Rheum. 42(11):2309-18.

Compston J, Cooper A, Cooper C (2009). Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. Maturitas, 62:105-108.

Compston JE (2007). Emerging consensus on prevention and treatment of glucocorticoid-induced osteoporosis. Curr. Rheumatol. Rep., 9: 78-84.

Cranney A, Guyatt G, Griffith L, Wells G, Tugwell P, Rosen C (2002). Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group**.** Meta-analyses of therapies for postmenopausal osteoporosis. IX: Summary of meta-analyses of therapies for postmenopausal osteoporosis. Endocrinol. Rev., 23:570-8.

Delmas PD (2002). Treatment of postmenopausal osteoporosis. Lancet, 359: 2018-2026.

Estell R (1998). Treatment of post menopausal osteoporosis. N. Eng. J. Med., 338: 736-746.

Fogelman I, Ribot C, Smith R (2000). Risedronate reverses bone loss in postmenopausal women with low bone mass: results from a multinational, double-blind, placebo-controlled trial. J. Clin. Endocrinol. Metab., 85: 1895-1900.

Grampp S, Henk CB, Fuerst TP, Lu Y, Bader TR, Kainberger F (1999). Diagnostic agreement of quantitative ultrasonography of tha calcaneus with dual X-ray absorptiometery of spine and femur. Am. J. Roentgenol., 173: 329-34.

Habiba, U., Ahmed, S., and L. Hassan (2002). Predisposition to osteoporosis in postmenopausal women. J Coll Physician Surg Pak., 12: 297-301.

Harris ST, Nelson B, Genant HK (1999). Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis. JAMA, 282.

Hooper M, Ebeling P, Roberts A (1999). Risedronate prevents bone loss in early postmenopausal women [abstract]. Calcified Tissue International (suppl 1), Abstract p. 80.

Hui SL, Slemenda CW, Johnston CC (1988). Age and bone mass as predictors of fractures in a prospective study. J. Clin. Invest., 81:1804-1809.

Lewiecki EM (2004). Management of osteoporosis. Clin. Mol. Alergy, 2: 9.

Lindsay R (2007). Beyond clinical trials: the importance of large databases in evaluating differences in the effectiveness of bisphosphonate therapy in postmenopausal osteoporosis. Bone, 40: 32-35.

McClung M, Clemmesen B, Daifotis A (1998). Alendronate prevents postmenopausal bone loss in women without osteoporosis. Ann. Intern. Med.,128: 253-261.

Melton LJ, Eddy DM, Johnston CC (1990). Screening for osteoporosis. Ann. Intern. Med., pp. 112-516.

National Osteoporosis Foundation (2003)**.** Physician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation

Nelson HD, Helfand M, Woolf SH, Allan JD (2002). Screening of post menopausal osteoporosis: A review of the evidence for the U.S. preventive services task force. Ann. Intern. Med., 137: 529-541.

Orwoll E (2000). Alendronate for the treatment of osteoporosis in men. N. Engl. J. Med., pp. 604-610.

Papaioannou A, Morin S, Cheung A (2010). 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ, 182: 1864-1873.

Peters ML, Leonard M, Licata AA (2001). Role of Alendronate and Risedronate in Preventing and Treating Osteoporosis. Cleve Clin. J. Med., 68: 945-951.

Reginster J, Minne HW, Sorensen OH (2000). Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Osteoporos Int., 11: 83-91.

Reid D, Hughes R, Laan RF (2000). Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial. J. Bone. Miner. Res., 15: 1006-1013.

Rosen CJ, Hochberg MC, Bonnick SL, McClung M, Miller P, Broy S (2005). Fosamax Actonel Comparison Trial Investigators. Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized double-blind study. J. Bone. Miner. Res., 20:.141-151.

Saag KG, Emkey R, Schnitzer TJ (1998). Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. N. Engl. J. Med., 339: 292-299.

Sambrook PN, Geusens P, Ribot C, Solimano JA, Ferrer-Barriendos J, Gaines K (2004). Alendronate produces greater effects than raloxifene on bone density and bone turnover in postmenopausal

women with low bone density: results of EFFECT (Efficacy of FOSAMAX versus EVISTA Comparison Trial) Int. J. Intern. Med., 255: 503-511.

Schneeweiss S, Avorn J (2005). A review of uses of health care utilization data for epidemiologic research on therapeutics. J. Clin. Epidemiol., 58: 323-337.

Silverman SL, Watts NB, Delmas PD, Lange JL, Lindsay R (2007). Effectiveness of bisphosphonates on nonvertebral and hip fractures in the first year of therapy: the risedronate and alendronate (REAL) cohort study. Osteoporos Int., pp.1825-1834.

Siris ES, Miller PD, Barrett-Connor E (2001). Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: Results from the National Osteoporosis Risk Assessment. JAMA, 286: 2815-2822.

Umer N, Syed Imran AS, Hammad NQ, Umair J, Salman S, Javed A (2003). An alternative tool to bone densitometry in ruling out osteoporosis in postmenopausal women between the age of 50 and 65 years. Pak. J. Med. Sci., 19(3): 178-181.

Van Staa TP (2006). The pathogenesis, epidemiology and management of glucocorticoid-induced osteoporosis. Calcif. Tissue Int., 79:129–137.

Watts NB, Worley K, Solis A, Doyle J, Sheer R (2004). Comparison of risedronate to alendronate and calcitonin for early reduction of nonvertebral fracture risk: results from a managed care administrative claims database. J. Manag. Care Pharm., 10: 142-51.

WHO report (1994). World Health Organization. Study group on assessment of fracture risk and its application to screening for post menopausal osteoporosis. Geneva: WHO 1994.