Treatment of Postmenopausal Osteoporosis By Evista (raloxifene) and Fasomax (alendronate)A Comparable study

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Abstract

Background :A new group of pharmaceutical substances for treatment of postmenopausal osteoporosis, named Selective Estrogen Receptor Modulators (SERMS). Evista (raloxifene) is the recent generation of SERMS, which acts through the binding with estrogen receptors in such a way that it acts as an estrogen agonist on bone and cardiovascular system while acting as an estrogen antagonist on breast and endometrium . Another new drug, named Fasomax (alendronate), is stable analog of inorganic pyrophosphate, which acts through binding to the bone mineral surface and inhibit osteoclastic bone resorption.

Objective : This study is focused to compare the effects of Evista (raloxifene) and Fasomax (alendronate) on the bone mineral density and bone quality in postmenopausal women with osteoporosis.

Methods: A prospective study done in Dar-Alshifa hospital (Abu-Dhabie), on 100 patients with postmenopausal steoporosis. These patients were randomized in two groups, Evista (raloxifene) and Fasomax (alendronate) treated groups, in both the results compared with a placebo group.Bone mineral density was performed regularly in our centre.Histomorphometry was performed on transiliac bone biopsy taken from volunteers in the central laboratory.

Results: In all treated patients whether by Evista(raloxifene) or Fasomax(alendronate), newly formed bone retained its normal lamellar structure, and there was no evidence for marrow fibrosis or cellular toxicity. The increase in bone mineral density was 4% with Evista and 16% with Fasomax.

Conclusion: Both Evista and Fasomax maintain the normal quality of bone. Evista has more extraskeletal beneficial effect esp. on lipid profile. Key words : evista, raloxifene, fasomax, alendronate, postmenopausal osteoporosis, histomorphometry, bone remodeling.

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Introduction :-

Menapause, apart from the bothersome short-term consequences (climacteric symptoms) that respond very well to short-term treatment of Hormone Replacement Therapy (HRT), has serious long-term consequences which include osteoporosis as well as deterioration of the lipid profile and increase in the risk for cardiovascular disease (CVD) and also increase risk for some cancers (mainly breast and endometrial cancer) .These long-term consequences of menopause require long-term therapy.[1]

Until recently HRT was considered the treatment of choice for the prevention of osteoporosis it seems that it may prevent also some of the other long-term consequences of menopause when given long enough . However, the compliance of postmenopausal women to HRT is very poor; Only about 5% of the Mediterranean countries and 8% in the USA receive HRT and 213 of those who receive discontinue treatment after one year . This low compliance is mainly due to fear of breast cancer and vaginal bleeding. It is for this reason that many physicians prescribe for osteoporosis treatment, one of the other antiresorptive drugs [2]. Current view, however , about the selection of the appropriate drug for osteoporosis management suggest that such medication should have a multi-target profile such as :-

-Efficacy against osteoporosis (prevention of the first but also of multiple new vertebral fractures).[3]

-other extraskeletal beneficial effects (lipid profile, CVD etc.)

-safety (breast, endometrium, general)

-good compliance of the patient, which depends on a simple and easy dose regimen, absence of serious side effects, especially from the gastrointestinal system, as well as good tolerance and continuation of the treatment [4].

Materials & Methods :-

Between August 2000 to June 2004, 100 patients with postmenopausal osteoporosis were seen at the out-patient clinic of our orthopaedic department in Dar-Alshifa hospital (Abu-Dhabie) .These women had osteoporosis with or without fractures and were randomized in two groups, i.e. Fasomax (alendronate) lOmg or 70mg , and 2nd group treated by Evista (raloxifene) 60mg or 120mg, in both the results were compared with a placebo group. All women received calcium 500mg, and vitamin D 400mg supplements per day.

The patients included in this study fulfilling the following criteria :-

1-Availability of the patients for interview and re-examination .

2- A minimum follow-up of 2.5 years .

3- All patients received vitamin D and calcium 500mg , per day .

4- Patients had to be at least 5 years post menopause .

5- Bone mineral density (BMD)[4], were performed regularly using dual-energy x-ray absorpiometry densiometers .Histomorphometry(5) was performed on transiliac bone biopsies[4] taken from osteoporotic patients in clinical trials of Evista and Fasomax after 2 and 3years of treatment.

6- Selected patients had to be generally in good health with absence of diseases or medications known to affect bone metabolism

Methods of assessment:-

Clinical assessment :-

To start with, patients had to be at least 5 years post menopause, and have a spine bone mineral density (BMD) below 0.80 glcm* using Hologic (Waltham) [4] or Norland (N. Brunswick, NJ) dual-energy x- ray absorptiometry densitometers, or 0.92 glcm* using Lunar[4] (Madison, WT) densitometers. In addition, eligible patients had to be in generally good health with absence of diseases or medications known to affect bone metabolism. Vitamin D deficiency was excluded by biochemical screening. The patients ,in this series, were randomized into two groups, 1st group recieved Evista (raloxifene) tablets, 60 or 120 mg and 2nd group received Fasomax (alendronate) tablets lOmglday or 70 mg/week

Out of 63 patients enrolled in the l st group, 9 patients were volunteers for a biopsy performed at the 24 -month time point.

Out of 47 patients enrolled in the 2nd group, 7 patients were volunteers for a biopsy performed at the 36 -month time point. A total of 16 biopsies were analyzed.

Biopsy procedure :

Transiliac bone biopsy(5) were obtained from consenting patients using a trephine needle (Meunier modification of Bordier trephine), with a minimum internal diameter of 7.5 mm. Before biopsy, patients received either 250 mg tetracycline four times daily, or 300 mg democlocycline twice daily (for 2days on, 12 days off, 2days on) with the last dose timed to occur 4-6 days before the biopsy. Bone specimens were transported in 70% ethanol to the central laboratory for the assessment and the analysis of biopsies .Only biopsies that provided a large enough area of intact cancellous bone were assessed quantitatively, as small samples can provide misleading data due to limited sampling. Inadequate biopsies were excluded from quantitative histomorphometric[5] analysis, but were included in the qualitative histological assessment, 5 biopsies from the 9 specimens examined in the 1st group and 3 biopsies from the 7 specimens examined in the 2nd group were adequate for quantitative analysis.

Qualitative analysis:

The appearance of the cellular components, the presence or absence of woven bone, or marrow fibrosis and any other noteworthy features were assessed qualitatively in all biopsies.(6)

Quantitative analysis:

The entire cancellous tissue area (including the transitional zone) of each section were analyzed(6). The following

parameters were measured :-

(a) osteoid volume 1 bone volume (OV1BV) was measured in cancellous bone on Goldner-stained sections, and expressed in percent of the cancellous bone volume .(7)

(b) osteoid surface 1 bone surface (OS1BS) was measured separately in cancellous and endocortical bone on Goldner-stained sections, and was expressed in percent of cancellous and 1 or endocortical bone surface.(6)

(c) Osteoid thickness (O.TH) was measured on Goldner-stained sections.(6)

(d) Mineral apposition rate (MAR)(4) was measured on unstained

sections under ultraviolet light and was expressed in mm/d.

To estimate the effects ofEvista or Fasomax on bone turnover at the site of biopsy, and to investigate the mechanism of action by which Evista or Fasomax induced the observed increase in bone density, the following parameters were measured:-

a- eroded surface (ES1BS) represents the percentage of the total bone i surface that consists of active (with the presence of osteoclast) or inactive (without osteoclast) eroded surface.(4)

b- Osteoclast surface (Oc.SlBS) represents the percentage of the total bone surface that consists of active eroded surfaces(4).

c- Osteoclast number (N.OclBS) is the number of osteoclasts per unit of bone surface.(4)

d- Erosion depth (E.De)(6) was derived after rebuilding of the

resorption cavity on an image analyzer. The computer automatically drew the trabecular surface. The operator rebuilt the resorption cavity by drawing a line with the help of the nonresorbed lamellae of the lacuna. Then, the analyzer automatically measured ES, the meanE.De (eight equidistant segments), and the maximam E.De .All resorption cavities were measured .

e- Eroded volume (EV1BV)[6] represents the amount of bone eroded as percent of cancellous bone volume, and was measured as described above.

f- The mineralizing surface was measured and expressed as a percentage of the total bone surface (MS1BS)[4]. The extent of the mineralizing surface was calculated as the length of the double-labeled surface plus half of the single-labeled surface.

g- Wall thickness (W.Th)[6]of cancellous packets was measured under polarized light. only completed packets were measured ,and measurements were performed on endocortical and cancellous bone separately.

h- Cancellous bone volume (BV/TV)[6] represents the percentage of spongy bone tissue including mineralized bone and osteoid.

i- Bone formation rate (BFR/BS)[6] was calculated as MSxMAR, and expressed in mm* 1mm*Id.

j- The activation frequency that represents the probability that a new cycle of remodeling will be initiated at any point of the bone surface was alculated as [6] (BFR1BS)/w.th, and was expressed per year.

k- Since the majority of erosion cavities were likely to have been incompletely resorbed at the time of biopsy, E.De is likely to underestimate the complete depth of erosion at the end of the resorption period. For this reason only an estimation of the bone balance at the basic multicellular unit level could be made by subtraction of E.De from W.Th.(6) With the exception of W.Th, these parameters were measured on Goldner-stained sections in endocortical and cancellous bone.

All parameters were measured by using a semiautomatic or automatic analyzer.

Statistical analysis :

for the primary endpoint (assessment of mineralization), a two-sided trend test was used to evaluate differences

among the treatment groups within each of the osteoporosis studies at a particular timepoint.

Mean and SD were computed for O.Th and MAR in each group ([4], where as median and SD of median were reported for OV1BV because of the nonnormal distribution of this latter parameter [4]. Mean and SD are reported for other parameters. Significance was declared at $p< 0.05$ for all parameters using two- sided testing.[4]

Strict random sampling was impossible because of the need for patient consent for biopsy separate from their consent to enter the clinical trials, and the p values reported are based on the reasonable assumption that data were similar to those that would have been obtained by a random sampling .[4]

Results :-

Patients with biopsies were comparable to patients who did not undergo bone biopsy in each study with respect to baseline characteristics (age, years after menopause, lumbar bone mineral density).Inadequate biopsies were predominantly due to the samples either being crushed or incomplete as a result of the biopsy procedure.

Effects on bone quality ;-

The qualitative assessment of bone did not reveal any abnormality that could reasonably be attributed to Evista or Fasomax therapy groups. Qualitative findings were reported in about 10% of the 16 biopsies at either 24 or 36 months (table 1) .Microcallus was seen in biopsies from two Fasomax-treated patients and one Evista-treated patient.

In all treated patients whether by evista or fasomax ,newly formed bone retained its normal lamellar structure, and there was no evidence for marrow fibrosis or cellular toxicity .

Table 1. Qualitative findings in biopsies obtained after 24 or 36 mo of treatment

	Placebo no. %	Evista no. %	Fasomax no. %
No.(%) with any	13 13.3	3 6.8	3 7.3
finding			
Lymphoid nodules	4 4.1	2 4.5	1 2.4
Very high remodeling	6 6.1	1 2.3	1 2.4
Microcallus[8]	1 1.0	0 0	1 2.4
Sarcoidosis[8]	1 1.0	0 0	0 0
/O\ Paget's disease	1 1.0	0 0	0 0

Effects on mineralization :-

Table 11 shows the results for the three predefined endpoints for assessment of mineralization. O.Th. was significantly lower in fasomax-and evista- treated patients .At each timepoint, the lowest values were consistently associated with the highest current dose of fasomax & evista. OV1BV decreased significantly with increasing dose of fasomax & evista . No consistent trends for changes in MAR related to treatment. These observations are consistent with the expected effects of a treatment-related decrease in the rate of bone turnover in the absence of any morphological or dynamic evidence of an impairment of mineralization.

Table 11. Effect of fasomax & evista on mineralization of bone

Treatment	placebo		fasomax		evista	
	n=31	%	n=9	%	n=15	%
O.Th	11.10	1.72	8.13	2.30	7.56	2.25
OV1BV	1.42	1.27	0.15	0.20	0.09	0.07
MAR	0.61	0.11	0.56	0.16	0.51	0.27

Effects on bone turnover (Table 111) :-

ES/BS and EV/BV showed no significant differences between treatment groups at either 24 or 36 months. At 24 months mean values for E.De (either maximam or mean) and for EV1BV tended to decrease . Similarly ,neitherOc.S/BS, nor N.Oc/BS showed any apparent response to treatment at either timepoint.

Fasomax & evista was associated with significantly lower OS/BS and MS/BS at each timepoint .Osteoid surfaces were higher in endocortical than in cancellous bone, in all groups . At 24 and 36 months, the BFR/BS and activation frequency were significantly decreased in all treated groups .

Effects on remodeling at the BMU level (Table 111):- In biopsies obtained at 24 mo, values for W.Th were significantly higher in patients receiving fasomax and evista. These data, however, need to be interpreted with caution as neither trend was apparent in analyses of biopsies obtained at 36 mo and the reduction of the daily dose from 20 mg to 5 mg between 24 and 36 mo may contribute to the loss of this effect.

Table 111. Effects of fasomax & evista on bone turnover

treatment	placebo		fasomax		Evista	
	n=31	%	n=9		n=9	%
BV1TV	16.1	0.8	16.9	1.6	15.2	1.1
W.Th	32	0.5	28.8	0.8	34.4	1.0
OS1BS	8.86	0.89	1.25	0.28	1.02	0.41
ES1BS	3.41	0.50	3.14		2.95	0.96
EV1BV	1.21	0.29	0.72		0.62	0.21
Oc.Lbs	0.31	0.07	0.18		0.43	0.25
N.Oc.Lbs	0.082	0.015	0.042	0.013	0.076	0.033
Max.E.De	15.79	0.91	13.97	1.06	12.92	0.84
Mean						
E.De	9.86	0.60	8.42	0.54	8.01	0.55

Discussion:-

Qualitative changes and effect on bone mineralization. From the qualitative assessment of bone biopsies in this study , it is evident that fasomax and evista treatment preserves the normal lamellar architecture of bone ,and did not induce woven bone, marrow fibrosis, cellular toxicity, or any others abnormality .

The observed decrease in OV without any changes in MAR provides evidence that fasomax and evista decreases the rate of bone turnover without inhibition of the mineralization in long-term clinical use[9]. Under steady-stats conditions with normal mineralization, the proportion of bone that remains unmineralized is directly proportional to the rate of bone turnover. The observed small decrease in O.Th is also probably accounted for by the decrease in the rate of bone turnover, although the precise mechanism for this effect remains to be determined[10]

This lack of effect on mineralization is highly consistent with other studies in animals and man. Thus, mineralization remained normal in patients with Pages't disease of bone who received 40 mg/d alendronate for 6 months[8]. In contrast, in rats, even the lowest antiresorptive dose of etidronate was associated with

defective mineralization, indicating a therapeutic ratio of 1:1 for this older alendronate [8,11]. This result is consistent with clinical experience of some centers, which have observed focal osteomalacia even with low dose (400mg/d) etidronate therapy.[4,8] The lack of adverse effect of alendronate on mineralization is most likely to be related to the small amount of drug absorbed. Even after 10 years of continuous daily treatment, the total skeletal load of alendronate is estimated to be only~80-100 mg distributed within 2-2.5 kg of bone mineral typically found in postmenopausal women[12].

Effect on turnover at the tissue level. Reflecting the expected decrease in the rate of osteoid and mineralizing surface, turnover bone formation rate and activation frequency decreased. The activation frequency was reduced by 88% after 2 yr of a daily dose of 10 mg, and by 93% after 3 years. proportional decrease in mineralizing surface in iliac bone relative to placebo in patients treated with fasomax and evista, however, was more marked (-90-95% at 2 yr) than the decrease in bone turnover in the skeleton as a whole as reflected by the biochemical markers. In the clinical studies, consistent decreases in biochemical markers of bone formation and resorption were -50% of baseline values[6,9,10]. The degree of suppression of turnover, however, may vary between different skeletal sites or different type of bone.

Although this difference could potentially be accounted for by some nonspecificity of the biochemical markers, it is clear that this is not case as, at least for TV-telopeptide cross links, high-dose antiresorptive treatment in healthy young men decreases the rate of bone resorption by at least 85%. Correspondingly, it seems likely that the relative degree of suppression is less in cortical bone, which constitutes at least 80% of the total bone mass in the body with lower remodeling rate than in cancellous and endocortical bone. The response to alendronate is similar in cancellous and endocortical areas. Even in iliac cancellous bone, there was no evidence that bone turnover was suppessed completely by any dose. Absence of detectable tetracycline label in the cancellous bone, following further sectioning where necessary, was noted in only tow biopsies, one of which came from a placebo-treated patient. These data are consistent with those from animal studies, in which even very high-

dose, long-term fasomax and vista reatment did not totally suppress bone turnover[10,11]

Table Iv. effects of fasomax & evista on endocortical & cancellous bone ;Mean (SEM)

	Results at 24 months						**Results at 36 months**					
treatment	**placebo**		**fasomax**		**evista**		**placebo**		**fasomax**		**evista**	
	n=31	**%**	**n=9**		**n=15**	**%**	**n=40**	**%**	**n=17**	**%**	**n=19**	**%**
OS1BS(%) Endocortical	11.07	1.36	1.71	0.54	2.10	1.31	12.74	1.13	1.76	0.45	3.23	0.65
OS1BS(%) cancellous	8.32	0.94	0.91	0.40	1.25	0.63	6.55	0.51	1.43	0.32	2.62	0.55

The histological observations confirm that the bone quality is preserved in patients receiving long-term therapy with either fasomax or evista. Therefore, the increase in bone density should be associated with both increased bone strength(11) and a reduction in fracture incidence(12) .Clinically important progressive increases in the bone density of the spine, hip, and total skeleton were observed over 3 years of treatment with fasomax and 2 years with evista, and these changes were associated with

a significant (48%) reduction in the proportion of patients with an incident vertebral fractures, as well as fewer patients with fractures at nonvertebral sites[4,6]. Recently, similar results were reported after 2 years of treatment at dose range of 1-5 mg daily for fasomax and a dose of 60-120 daily for evista[12].

The other aspects of the present study were more exploratory in nature . All of the clinical studies indicate that both fasomax and evista induced marked increases in bone density that are most rapid during the first 6-12 months, following which there is a slower, but sustained and virtually linear increase in BMD of the spine and proximal femur for at least 36 months. The early increase is most probably explained, at least in large part, by the filling in of the remodeling space due to the early decrease in the rate of turnover at the tissue level, but a reduction of bone loss can continue during the low turnover steady state induced by fasomax and evista [1,12]. Similarly,fasomax had surprisingly little detectable effect on bone resorption parameters, including eroded surface ,volume and osteoclast number.Evista clearly has marked effect to inhibit bone resorption, which is evidenced by decreased urinary excretion of bone collagen breakdown products, the small changes in erosion parameters are difficult to interpret. This difficulty may result from a prolongation of the reversal phase of the remodeling cycle, a decreased erosion rate, the imprecision of histomorphometric resorption endpoints, or a higher effect in cortical than cancellous bone.

The effect of fasomax or evista on osteoclast apoptosis remains unclear. Although previous studies suggested that evista may only inhibit resorption activity[12] (which may explain the maintenance of osteoclast number) a recent paper reported that fasomax was capable of inducing osteoclast apoptosis[11].

Effect on bone balance at the basic structure unit level. The continuing, progressive increase in BMD suggest that there is an additional effect of treatment to reverse the negative balance at the level of the individual bone remodeling unit. Such an effect could result from a decrease in erosion depth, an increase in the wall thickness, or a combination of the two. Unfortunately, erosion depth can not be measured directly, because the preexisting surface has vanished. Attempts to estimate erosion depth, such as the method used in the current study , make assumptions about the position of the previous surface from the remaining contours[4]. Such estimates are, at best, imperfect[4,12]. Alternative methods, such as counting the number of transected lamellae, also suffer from practical difficulties and are not easily replicated.[12]

The data from the 24- months biopsies did indeed suggest that, at the 10-and 20-mg doses , fasomax and 60-, 120- mg doses, evista increases W.Th and tends to decrease E.De. These effects may have resulted in a positive bone balance at the basic structure unit (BSD) level, thereby potentially accounting for the progressive increase in bone density. Whereas W.Th was measured on complete packets[5], E.De was measured in sites where resorption was ongoing and at different stages of completion, which explains why mean W.Th was approximately threefold greater than mean E.De. Thus, although the trend towards an increase of bone balance at the tissue level seems to be the most likely explanation for the progressive gain in BMD, the data from the current study obtained at the BSU level are equivocal, and a larger number of biopsies would be required to confirm this hypothesis. A loss of the effect of fasomax and evista at 36months could not be excluded.Potential effects on the mineralization.

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