Bone 44 (2009) 1049–1054

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Bazedoxifene reduces vertebral and clinical fractures in postmenopausal women at high risk assessed with FRAX®

John A. Kanis *, Helena Johansson, Anders Oden, Eugene V. McCloskey

WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, Beech Hill Road, Sheffield S10 2RX, UK

ARTICLE INFO

Article history:
Received 14 August 2008
Revised 5 February 2009
Accepted 11 February 2009
Available online 28 February 2009

Edited by: R. Baron

Keywords:
FRAX
Bazedoxifene
Fracture probability
Randomised controlled trial
Clinical fractures

ABSTRACT

Introduction: Bazedoxifene has been shown to significantly decrease the risk of vertebral fractures in postmenopausal women. No significant effect was noted on the risk of clinical fractures, but fracture risk reduction was reported in a *post hoc* subgroup analysis in a high risk group categorised on the basis of BMD and prior fracture.

Aims: The aim of this study was to re-evaluate the efficacy of bazedoxifene on fracture outcomes avoiding subgroup analysis by examining the efficacy of intervention as a function of fracture risk.

Methods: The phase III study was a double-blind, randomised, placebo- and raloxifene-controlled randomised 3-year multinational study that enrolled 7492 osteoporotic women aged 55 years or more (mean age = 66 years). For the present analysis, women taking raloxifene were excluded ($n = 1849$), and we compared the effects of two doses of bazedoxifene (20 and 40 mg daily combined) with placebo on the risk of all clinical fractures as well as the risk of morphometric vertebral fracture. The risk of a major osteoporotic fracture was assessed using region specific FRAX® algorithms, and the relationship between pre hoc 10-year fracture probabilities and efficacy examined by Poisson regression.

Results: Overall, bazedoxifene was associated with a significant 39% decrease in incident morphometric vertebral fractures (hazard ratio HR = 0.61; 95% CI = 0.43–0.86; $p = 0.005$) and a non-statistically significant 16% decrease in all clinical fractures (hazard ratio HR = 0.84; 95% CI = 0.67–1.06; $p = 0.14$) compared to placebo. Hazard ratios for the effect of bazedoxifene on all clinical fractures decreased with increasing fracture probability. In patients with 10-year fracture probabilities at or above 16%, bazedoxifene was associated with a significant decrease in the risk of all clinical fractures. The 16% probability threshold corresponded to the 80th percentile of the study population. Hazard ratios for the effect of bazedoxifene on morphometric vertebral fractures also decreased with increasing fracture probability. In patients with 10-year fracture probabilities above 6.9% (corresponding to the 41st percentile), bazedoxifene was associated with a significant decrease in the risk of morphometric vertebral fractures. At equivalent fracture probability percentiles, the treatment effect of bazedoxifene was greater on vertebral fracture risk than on the risk of all clinical fractures. For example, at the 90th percentile of FRAX® probability, bazedoxifene was associated with a relative risk reduction of 33% (95% CI = 7–51%) for all clinical fractures and 51% reduction (95% CI = 21–69%) for morphometric vertebral fractures. The findings were robust to several sensitivity analyses.

Conclusion: Bazedoxifene (20 and 40 mg doses combined) significantly decreased the risk of all clinical fractures and morphometric vertebral fractures in women at or above a FRAX® based fracture probability threshold. These results, consistent with the previous subgroup analysis, suggest that bazedoxifene should be targeted preferentially to women at high fracture risk.

Introduction

Bazedoxifene acetate is a new chemical entity, and on the basis of biochemical, in vitro cellular, and in vivo data, can be considered a mixed-function estrogen that demonstrates tissue selectivity. Pre-clinical and clinical studies suggest that it exerts estrogenic activity on bone without adverse effects on breast and uterine tissue [1–4]. This profile prompted the development of bazedoxifene for the prevention of fractures in postmenopausal women. The principal phase III study was designed to elucidate the effect of this agent on vertebral fracture risk in postmenopausal women with osteoporosis as a primary outcome [5]. A secondary endpoint was the effects of bazedoxifene on the risk of non-vertebral fractures.

The trial showed a significant effect of bazedoxifene on vertebral fracture risk for each of the two doses tested. Bazedoxifene 20 mg daily decreased the risk of morphometric vertebral fractures by 42% (hazard ratio, HR = 0.58 (95% confidence interval, CI = 0.38–0.89) and

* Corresponding author. Fax: +44 114 285 1813.
E-mail address: w.j.Pontefract@shef.ac.uk (J.A. Kanis).

8756-3282/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.bone.2009.02.014

a similar effect was noted with a 40 mg daily dose (HR = 0.63; 95% CI = 0.42–0.96). There was no significant effect on non-vertebral fractures, even when data from the two doses were combined (HR = 0.89; 95% CI = 0.70–1.14) [6]. A *post hoc* analysis in a subgroup of patients at high risk (femoral neck T-score ≤ −3 SD and or ≥1 moderate or severe, or multiple mild vertebral fractures) reported that bazedoxifene 20 mg daily reduced the incidence of non-vertebral fractures by 50% compared to placebo (HR = 0.50; 95% CI = 0.28–0.90; $p = 0.020$). The effect of the higher dose was not significant (HR = 0.70; 95% CI = 0.41–1.20). A significant effect was seen with the two doses combined (HR = 0.60; 95% CI = 0.37–0.95), but the subgroup analysis lost power to detect a significant effect on vertebral fracture of the 20 mg dose (HR = 0.50; 95% CI = 0.24–1.03), though a significant effect was seen with the two doses combined (HR = 0.54; 95% CI = 0.30–0.98) [6].

There are obvious difficulties with *post hoc* analyses. These are particularly acute when undertaken on subgroups, and in subgroups that may be difficult to justify on clinical grounds. The *post hoc* nature, the change in the significance of the primary outcome, and the way of categorising the high risk group based on femoral neck T-score and prevalent vertebral fracture status weaken the validity of the analysis and the conclusion that bazedoxifene is effective in decreasing the risk of non-vertebral fractures.

Against this background the present study, although it cannot avoid *post hoc* status, aimed to avoid subgroup analysis and the associated loss of statistical power. The specific aim was to apply multivariate models to the entire study population to assess the efficacy of bazedoxifene on both all clinical fracture outcomes and on morphometric vertebral fracture risk. This analysis incorporated a clinically relevant metric of high risk as a continuous variable (the FRAX® tool for fracture probability) as requested for new phase III studies by the Committee for Medicinal Products for Human Use (CHMP) [7]. The hypothesis tested was that bazedoxifene reduced the risk of fracture in women with the higher fracture probabilities assessed at study entry.

Methods

The osteoporosis study

Details of this study are published elsewhere [5]. In brief, the multinational study included women from the Asia/Pacific countries, Canada, Europe, Latin America, South Africa, and the United States. The study was double-blind, randomised, placebo- and raloxifene-controlled study including 7492 osteoporotic women aged 55 years or more (mean age = 66 years). The primary analysis was over a three year exposure. The study was extended twice; each extension was for 2 years. The first 2-year extension is to be completed in September 2008.

Postmenopausal women were recruited either on the basis of low BMD (T-score < −2.5 SD at the lumbar spine or femoral neck) or a prior vertebral fracture. Patients were randomised to four treatment groups: Two groups received bazedoxifene (20 or 40 mg daily; $n = 1886$ and 1872, respectively), a third group received raloxifene (60 mg daily), and a placebo group ($n = 1885$). All patients took calcium (1200 mg daily) and vitamin D (400–800 IU daily). The primary endpoint of the 3-year study was to evaluate efficacy of bazedoxifene compared with placebo on the risk of radiographically confirmed new vertebral fractures in postmenopausal women with osteoporosis after 36 months of therapy. A secondary endpoint was the effect of bazedoxifene on non-vertebral fracture and clinical vertebral fractures. For the purposes of this analysis, women taking raloxifene were excluded ($n = 1849$), and we compared the effects of two doses of bazedoxifene (20 and 40 mg daily combined) with placebo on the risk of all clinical fractures as well as the risk of morphometric vertebral fracture.

Assessment of fracture risk

Ten-year fracture probability was assessed with the FRAX® tool in placebo and bazedoxifene treated patients. FRAX® is a computer based algorithm (http://www.shef.ac.uk/FRAX) that provides models for the assessment of fracture probability in men and women [8–10]. The approach uses easily obtained clinical risk factors to estimate 10-year probability of a major osteoporotic fracture (hip, clinical spine, forearm or humerus) or of a hip fracture. The former was chosen as the risk variable and the latter used in a sensitivity analysis. The estimate of probability can be used with clinical risk factors alone, or with femoral neck BMD. Since fracture risk prediction is enhanced with the input of BMD [11], BMD was included.

Probability of fracture is calculated in women from age, body mass index (BMI) computed from height and weight and dichotomised risk variables that comprise;

a prior fragility fracture,
parental history of hip fracture,
current tobacco smoking,
ever long-term use of oral glucocorticoids,
rheumatoid arthritis,
other causes of secondary osteoporosis,
daily alcohol consumption of 3 or more units daily.

Characterisation of risk factors

Age was available for all patients. Height and weight for the estimation of BMI were available in 7479 women of 7492 women (99.8%). The characterisation of other relevant risk factors (listed above) is summarised below.

Previous fracture — a history of a previous fracture of any kind was reported in 1264 patients. To this was added the finding of a greater than grade I (mild) morphometric vertebral fracture at baseline. In total 2360 patients were considered to have a prior fracture (32%). Patents with a single mild morphometric vertebral fracture ($n = 2728$) were excluded, because there is uncertainty over the clinical significance of low-specificity definitions of vertebral fracture [12,13]. Moreover, an analysis within the present study confirmed the weak predictive value of this risk variable as shown in Table 1. Moderate ($n = 709$) and severe ($n = 7$) fractures were associated with a significant increase in the risk of a further clinical fracture in the whole study population and in placebo treated patients alone. There was no significant increase in the risk of a clinical fracture in patients with a mild vertebral fracture. These associations persisted with adjustment for femoral neck BMD. Similar findings were noted with respect to the prediction of morphometric vertebral fracture (data not shown).

Parental history of hip fracture — No information was available from the dataset and this variable was simulated. The simulation was

Table 1
Hazard ratios for the prediction of all clinical fractures according to the grade (severity) of a prior vertebral fracture

Grade of prior vertebral fracture	Placebo treated patients			All patients		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
(a) Without BMD						
None	1.0			1.0		
Mild	0.90	0.60–1.35	>0.30	1.10	0.89–1.35	>0.30
Moderate/severe	2.15	1.29–3.58	0.0034	1.65	1.22–2.25	0.0014
(b) With BMD						
None	1.0			1.0		
Mild	1.00	0.65–1.54	>0.30	1.22	0.98–1.52	0.079
Moderate/severe	2.22	1.30–3.77	0.0033	1.70	1.24–2.33	<0.001