Oyágüez Martín I[1], Gómez Alonso C[2], Marqués de Torres M[3], García Coscolín T[4], Betegón Nicolás L[4], Casado Gómez MA[1]

1 Pharmacoeconomics & Outcomes Research Iberia - Madrid

2 Servicio de Metabolismo Óseo y Mineral - HUCA - Oviedo

3 Farmaceútico de Atención Primaria - Area Sanitaria Este de Málaga-Axarquia

4 Departamento Economía de la Salud - Sanofi-Aventis - Madrid

Evaluation of the risedronate efficiency 75 mgs versus generic alendronate 70 mgs, in women with post-menopausal osteoporosis and previous vertebral fractures in Spain

Correspondence: Itziar Oyágüez - Pharmacoeconomics & Outcomes Research Iberia - Segundo Mata, 1 - 28224 Pozuelo de Alarcón - Madrid (Spain)
e-mail: ioyaguez@porib.com

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Summary

Introduction: The objective is to assess the cost-effectiveness of risedronate 75 mg 2 consecutive days/month vs generic alendronate 70 mg weekly, during one year in 75 years old females with post-menopausal osteoporosis and previous vertebral fracture.

Methods: A cost-effectiveness analysis under Health National System perspective has been developed to assess clinical (hip fracture prevention and quality adjusted life years gained) and economic consequences (€ 2010) during 5 years following one year treatment with both alternatives. Drug effect has been considered during the one year of drug administration. Epidemiology data and unitary costs were derived from Spanish literature.

Results: In a cohort of 1.000 females, (75 years old) with post-menopausal osteoporosis and vertebral fractures, risedronate 75 mg vs alendronate avoid 10 hip fractures, with 9.983€/hip fracture avoided cost. Aditional QALY gained are 4 with an incremental cost of 99,83€. Incremental cost-effectiveness ratio (ICER) is 24.957€ per QALY gained with risedronate 75 mg vs generic alendronate 70 mg.

Conclusion: In the treatment of females with post-menopausal osteoporosis and previous vertebral fracture, risedronate 75 mg 2 consecutive days/month compared to generic alendronate 70 mg weekly is an efficient strategy in Spain.

Key words: *Osteroporosis, Risedronate, Alendronate, Costs.*

Introduction

Osteoporosis constitutes a significant public health problem, with a great clinical and economic impact[1]. In Spain, 25% of women aged between 60 and 69 years, and 40% between 70 and 79 years, have osteoporosis[2].

A Spanish study carried out locally, found that the prevalence of vertebral fracture in people over 50 years varies between 17.4 and 24.6% depending on the radiological criteria used, this prevalence increasing with age. In fact the number of fractures practically doubles for each 10 years of age[3].

Within osteoporotic fractures, hip fractures are those with the strongest direct link to osteoporosis, due to their serious clinical consequences, their higher requirement for days of rehabilitation and costs of hospitalisation[4,5]. It is estimated that there are, globally, 1.6 million hip fractures annually, which could reach 4.5 million in the year 2050[5,6].

The biphosphonates are considered to be the medicines of first choice in the treatment and prevention of osteoporotic fractures[7], but a significant percentage of women with osteoporosis discontinue treatment, or do not adhere to it[8], due to the dosage, frequency of administration and the occurrence of adverse events. The discontinuation and lack of adherence to treatment are associated with an increase in the risk of fractures[9-11] and in health costs[12]. The relationship between the cost of treatments for osteoporosis and the results obtained by their use (number of fractures avoided and survival in quality adjusted life years) is a relevant factor in taking decisions in clinical practice[13].

The aim of this evaluation has been to estimate, from the health perspective, the Incremental cost-effectiveness *ratio* (ICER) relationship between the biphosphonates 75 mg risedronate for 2 consecutive days/month and 70 mg generic alendronate weekly, administered for a year, in women over 75 years of age with OPM and PVF.

Methods

Patients

The profile of the population analysed in this economic evaluation is: women of 75 years of age, with a bone mineral density of ≤ -2.5 SD (T-score < -2.5) and with FVP.

The case base of the analysis centres on a hypothetical cohort of 1,000 patients, although a sensitivity analysis was also carried out which showed the results applied to the female Spanish population from 65 to 80[14], to which was applied the rate of osteoporosis[15], which were weighted into 8 different strata due to the presence or not of PVF[16].

Compared treatments

The alternative therapies compared were: 75 mg risedronate for 2 days consecutively/month for a year, against 70 mg generic alendronate weekly over a year.

Effectiveness of the medicines

The evaluation of the efficiency of medicines requires the estimation of their effectiveness. In this case, the data on effectiveness are obtained from a sub-analysis of the REAL (the RisedronatE and ALendronate study) study[17]. The REAL study[18], is a retrospective observational cohort study in which are compared the effectiveness of weekly administration of alendronate with risedronate in the reduction of vertebral and hip fractures. The effectiveness of generic alendronate included in the economic evaluation was considered to be equivalent to the original alendronate which was administered in the REAL study[18].

Economic analysis

The calculation of the efficiency comparison between risedronate and alendronate was carried out by means of the ICER[19] relationship between the two alternatives using the following formula:

$$ICER = \frac{\text{COST OF RISEDRONATE} - \text{COST OF ALENDRONATE}}{\text{EFECTIVENESS OF RISEDRONATE} - \text{EFECTIVENESS OF ALENDRONATE}}$$

The costs of each of the therapies include the total costs of treatment and of fractures.

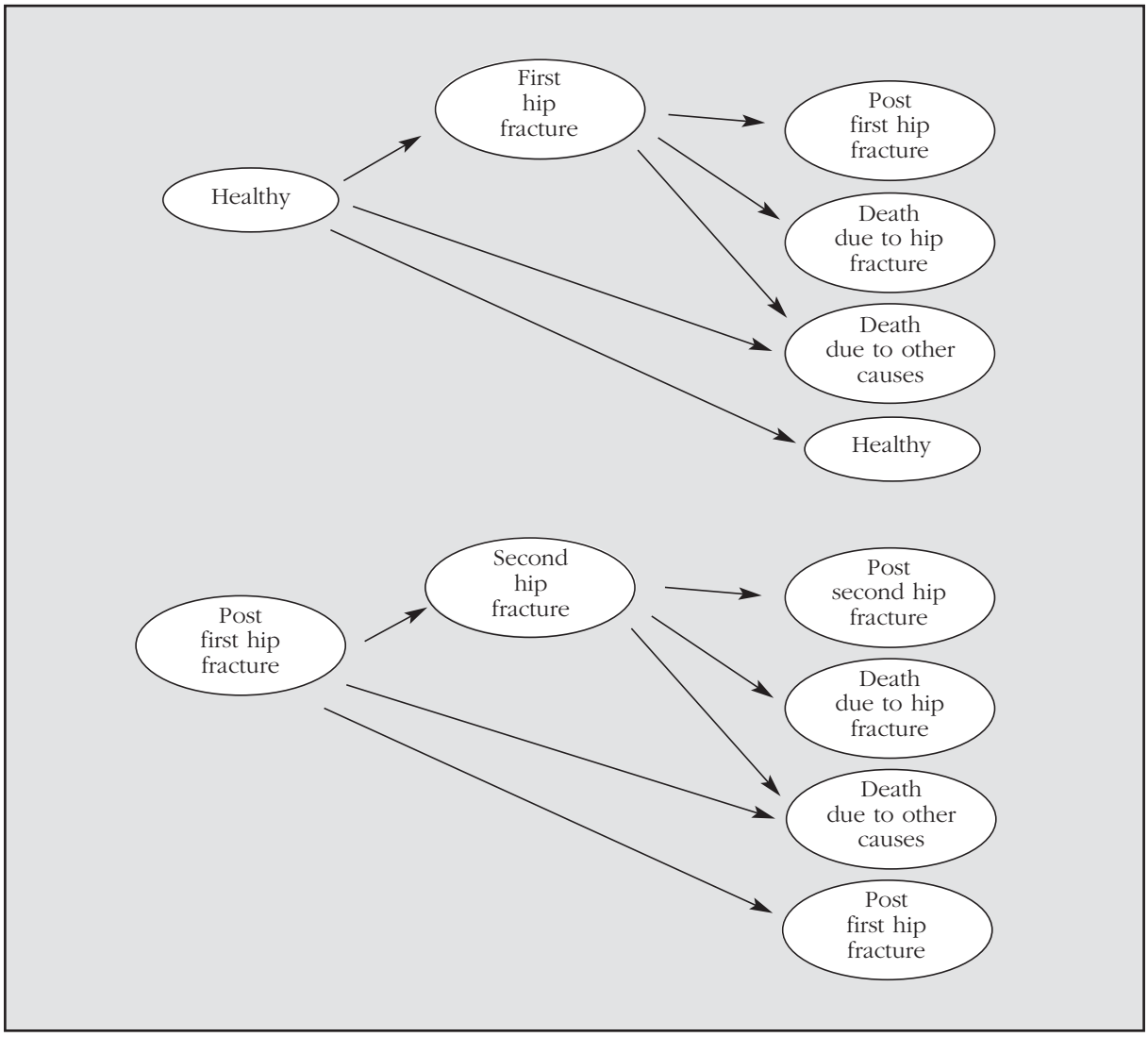
To measure the effectiveness, the number of hip fractures avoided (using the incidence of fractures according to age and the efficacy of each medicine), and life years for quality adjusted life years (QALY) gained by each alternative, was used.

To determine whether the adoption of an alternative has a reasonable increased cost in relation to the increase in effectiveness achieved, in the cost-utility analysis the maximum efficiency or cost threshold was defined as that cost which it was prepared to be paid for each additional unit of effectiveness achieved with one therapeutic option compared with another. In this study the efficiency threshold was considered to be 38,000€ per quality adjusted life year. This value was obtained by updating to the year 2010, using the general consumer price index[20], the normally accepted threshold value for economic evaluation in Spain, (30,000€ per year of life gained in the year 2000)[21], and which agrees with the recommendations for Spain of other authors which place the threshold in a range between 30,000 and 45,000€ for each quality adjusted life year gained[22]. In addition, a threshold has recently been established in a series of countries, among which Spain is included, for health interventions indicated for the treatment of osteoporosis[23]. This threshold, specific for the interpretation of results in osteoporosis in Spain, has been positioned at 47,000US$, equivalent to 34,768€, (using an exchange rate of 1 euro = 1.3518 US$, at 15th May 2009; ECB)[24].

Model

The economic analysis of risedronate compared with alendronate was carried out using Markov's model, which had allowed the estimation of the long term (5 year) clinical and economic consequences of the administration of the two treatments compared with a hypothetical cohort of 1,000 patients.

Figure 1. Description of Markov model



The Markov models are characterised by their requirement for the definition of different states of heath between which the patients may move. The model used in this study includes 4 different health states:

-Healthy (not having suffered any hip fractures).

-Hip fracture (first or second).

-Post-fracture of the hip (first or second).

-Death (whether due to hip fracture, or for other reasons).

Figure 1 shows a schematic representation of the model used.

Among the premises contained in the model, notable is the fact that discontinuations in treatment have not been taken into account, which means that the pharmacological cost of the therapy evaluated refers to the pharmacological cost of a complete year of treatment for each patient. In addition, any residual effects of the drugs have not been considered, rather, it has been assumed that the medicines only had an effect during the year of administration.

Estimation of costs

All the costs included in the analysis are given in euros (€, at 2010 value). The evaluation was carried out from the perspective of the Spanish National Health System, which means that only the direct health costs associated with the therapies have been considered.

The pharmacological cost was calculated from the retail cost plus VAT of the medicines, for generic alendronate, taking into account the stipulations of the Law of Royal Decree 4/2010[25]. The cost of hip fractures was obtained from the literature[26].

Table 1 includes the values of the relevant parameters and the unit costs used in the analysis.

In agreement with current recommendations[27] a discount rate of 3% has been applied to the costs and benefits.

Sensitivity analysis

The sensitivity analysis to confirm the stability of the model was carried out, having:

-Obtained results for the Spanish female population of between 65 and 80 years of age (from 8 different strata), with OPM, weighted with/without PVF, and taking into account mortality due to hip fracture[28].

-Considered the residual efficacy during the year following the end of the year of treatment.

Results

The administration of 75 mg risedronate for 2 consecutive days/month for a year in a cohort of 1,000 women of 75 years of age with OPM and PVF avoided 10 more hip fractures than the administration of 70 mg generic alendronate weekly for a year.

The cost of each additional hip fracture avoided with 75 mg risedronate vs alendronate is 9,983€.

In the cohort of 1,000 women 2,919 QALYs were achieved with 75 mg risedronate, compared with 2,915 with alendronate, which means an additional gain of 4 QALYs with the risedronate therapy, with a total increased cost of 99.83€ . The cost for each gain in QALY with risedronate as against alendronate is 24,957.50€ (Table 2).

The results in the Spanish population females of between 65 and 80 years of age with OPM, aggregated and weighted as a function of 8 different strata, with or without PVF, show that the increase in cost per QALY gained with 75 mg risedronate for 2 consecutive days/months is cost-effective in comparison with 70 mg generic alendronate weekly, being 32,827 per QALY.

The cost/additional QALY of risedronate, as against alendronate, is 13,374€/QALY in the population with PVF and 41.481€/QALY in the population without PVF.

When the residual effect of the therapies after the end of the year of treatment is taken into consideration, the cost per hip fracture avoided with 75 mg risedronate for 2 consecutive days/month as against 70 mg generic alendronate weekly is 3,266€ and the cost per QALY gained is 8,065€/QALY with risedronate vs alendronate.

The results in the Spanish population between 65 and 80 years of age, weighted as a function of 8 different strata, with or without PVF, taking into consideration the existence of residual efficacy, estimate that the cost/additional hip fracture avoided is 12,241€ and the cost/QALY is 25,488€/additional QALY with 75 mg risedronate vs generic alendronate.

Table 3 shows the detailed results of all the sensitivity analyses carried out.

Discussion

Osteoporosis, in recent years, has consolidated its position as one of the major socio-health problems in Spain, both due to its high prevalence and for the economic costs which it generates.

Various studies have provided evidence that therapy with risedronate reduces the risk of fracture in women with osteoporosis[29-32], even in the first 6 months of treatment, giving it an added advantage over other biphosphonates[18].

In women over 75 years of age with OPM and PVF therapy with 75 mg risedronate for two consecutive days/month is more effective than therapy with 70 mg generic alendronate weekly, since more hip fractures are avoided and the patient benefits from a greater number of quality adjusted life years.

The efficiency of the treatments for osteoporosis, that is to say, the relationship between their cost and the health benefits resulting from their use (reduction in risk and number of fractures avoided, and survival in quality adjusted life years), should be a key factor in taking decisions in normal clinical practice.

In comparison with 70 mg generic alendronate weekly, 75 mg risedronate for 2 consecutive days/month, is an efficient therapy (cost-effective alternative). The study was based on an efficiency threshold of 38,000 euros per quality adjusted life year gained, derived by updating threshold of Sacristan et al. in values for 2009, of 38,220 euros[21], and the average of the threshold range established by De Cock et al., of 37,500 euros[22]. These values are close to the threshold determined for Spain in the treatment of osteoporosis of 34,768 euros[22]. The authors of this international study recommend the use of this threshold in the pharmacotherapeutic guides, in combination with algorithms for the prediction of risk of fractures, to be used in taking decisions with the aim of carrying out an efficient selection of patients suitable for treatment. The efficiency threshold varied between the different countries as a function of the availability of funding for each quality adjusted life year, the costs associated with fractures and the costs of health interventions used to reduce the risk of fracture[23].

The results, aggregated and weighted in 8 strata representative of women of between 65 and 80 years of age according to the rate of osteoporosis and the incidence of PVF in Spain, confirmed the robustness and consistency of the results.

When the residual effects of the therapies at the end of the year of treatment are taken into consideration, the cost-utility of 75 mg risedronate vs alendronate is only 8,065€/QALY and continues to be below the accepted efficiency threshold.

This analysis considers treatments of a complete year for each of the therapies. Adherence, with its two facets: compliance and persistence, is a key factor for being able to extrapolate the efficacy of the biphosphonates demonstrated in the clinical trials into clinical practice[33,34], since the inadequate adherence to treatment has been associated with increase of 17% in the risk of fracture 10 and even 37% in the risk of hospitalisation for any cause[35].

In addition to deteriorations in the state of health, poor compliance and low persistence are also associated with a reduction in the efficiency of the therapies[36]. Adequate compliance, with rates from 50% and mainly of 75%[37], are directly related to changes in bone mineral density in those patients, which as an important marker for bone turnover, is considered a good predictor for the reduction in risk of fractures. Adherence is therefore a challenge for clinicians involved in the treatment of osteoporosis[32]. Those medicines with the simplest and most time-spaced dosage regimens are better accepted by patients, ensuring greater compliance with the therapies[38,39].

Table 1. Principal variables of case base of model

Parameter	Value	Reference
Epidemiological data		
Rate of osteoporosis in Spain		(2)
60-69 years	24.29%	
70-80 years	40.00%	
Incidence of hip fractures (expressed per 10,000 inhabitants)		(15)
50-69 years	13.8	
70-74 years	30.5	
75-79 years	65.1	
80-84 years	124.4	
85-89 years	213.2	
90-94 years	302.2	
95-100 years	432.8	
Prevalence of vertebral fracture		(16)
50-54 years	11.50%	
55-59 years	14.60%	
60-64 years	16.80%	
65-69 years	23.50%	
70-74 years	27.20%	
>75 years	34.80%	
Mortality in year following a hip fracture	Relative risk	(28)
50-54 years	8.26	
55-59 years	6.69	
60-64 years	5.44	
65-69 years	4.41	
70-74 years	3.58	
75-79 years	2.74	
80-84 years	2.09	
85-89 years	1.74	
>90 years	1.46	
Effectiveness (reduction in hip fractures)		
Risedronate	50%	(18)
Alendronate	10%	(18)
Cost data		
Hip fracture (first year)	7,438€	(26)
Hip fracture (successive years)	1,487.66€	(26)
75 mg risedronate – retail cost, plus VAT/day	1.1553€	
70 mg alendronate – retail cost, plus VAT/day	0.5507€	(25)

Table 2. Results of the cost/utility analysis in the case base (women older than 75 years of age with postmenopausal osteoporosis and previous vertebral fracture)

	Risedronate	Alendronate	Risedronate vs Alendronate
Hip fractures (per 1,000 women)	99	109	10
QALY (per 1,000 women)	2,919	2,915	4
Total costs (€/per 1,000 women)	1,354,200	1,254,370	99,83
Avoided cost per hip fracture (€)			9,983
Cost per QALY gained (€)			24,957.50

QALY: quality adjusted life year

The premise of total adherence to treatment adopted in the current analysis makes a conservative assumption for risedronate, since its monthly administration has demonstrated significant improvements with respect to the weekly administration of alendronate in adherence to treatment with biphosphonates in women with OPM, with a compliance of 74% with monthly risedronate, as opposed to 66% with weekly therapy with alendronate[40].

The consideration of a higher adherence to risedronate therapy would not have been able to have been extrapolated from the effectiveness data from the REAL study[18], which excluded the same proportion (41%) of patients in both treatment groups for not complying with the minimum period for adherence established in the trial's protocols (3 months).

The efficiency of 35 mg risedronate as opposed to 70 mg of generic alendronate, both administered weekly, has previously been established in the Spanish environment[41]. Possible methodological differences, as well as the reference years for the costs, and differences in medical practice are a barrier to direct comparisons with estimates of efficiency obtained in other countries. Even so, illustratively, it has been found that monthly therapy with risedronate is considered to be cost-effective in comparison with weekly alendronate, by other authors, with estimates of 9,476$/QALY (US)[42].

The model used in this work, informed by the REAL study, has been used in economic evaluations of risedronate vs alendronate in other environments with women over 65 years of age, reaching similar conclusions in terms of efficiency to those we obtained in our analysis, with values of 3,877$/additional QALYs obtained by risedronate compared with alendronate in Canada (values for 2006)[43] and dominant in studies carried out in Italy (values for 2006)[44], and Germany (values for 2008)[45].

As limitations and possible bias in this economic evaluation, should be mentioned the inherent theoretical nature of any type of modelling which, on occasions, does not give results which reflect clinical practice.

The validity of an economic model is conditional on the quality of the data on which it is based. In our case, the principal source of information was the REAL study, a retrospective observational study with a level of data lower than that of a clinical trial, due to the possible existence of differences in the characteristics of the cohorts which are compared. However, the use of data from randomised clinical trials is also arguable, due to the rigidity of the inclusion criteria which do not make them representative of normal clinical practice, principally when data from multinational studies are used in economic evaluations at a local level[46].

In conclusion, our results demonstrate the efficiency of therapy with 75 mg risedronate for 2 consecutive days/monthly compared with 70 mg generic alendronate weekly in the treatment of women over 75 years of age with OPM in Spain.

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Table 3. Results of the analyses of sensibility realized

Without residual efficacy			**Cost/QALY**
	Spanish population (a) (b)		
		Results (population with PVF) (c)	
		Cost/avoided hip fracture (with FVP)	6,322€
		Cost/QALY (with PVF)	13,374€
		Results (population without PVF)	
		Cost/avoided hip fracture (without FVP)	29,997€
		Cost/QALY (without FVP)	41,481€
		Weighted results with/without PVF	
		Cost/avoided hip fracture	22,707€
		Cost/QALY	32,827€
With residual efficacy			
	Hypothetical cohort (1,000 women > 75 years of age with PVF)		
		Cost/avoided hip fracture	3,226€
		Cost/QALY	8,065€
	Spanish population (a) (b)		
		Results (population with PVF) (c)	
		Cost/avoided hip fracture (with FVP)	3,089€
		Cost/QALY (with PVF)	6,503€
		Results (population without PVF)	
		Cost/avoided hip fracture (without FVP)	16,313€
		Cost/QALY (without FVP)	33,935€
		Weighted results with/without PVF	
		Cost/avoided hip fracture	12,241€
		Cost/QALY	25,488€

(a): female population in 2009[14]
(b): rate of osteoporosis[2]
(c): rate of incidence of previous vertebral fracture in women[16]
QALY: quality adjusted life years
PVF: previous vertebral fracture

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