Author’s response to reviews

Title: Cost of non-persistence with oral bisphosphonates in post-menopausal osteoporosis treatment in France

Authors:

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Author’s response to reviews: see over
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**Date:** 30 March 2011  
**Reviewer's report:**  
The purpose of this study is a real hot topic for osteoporosis, a public health problem related to its high incidence and prevalence and the high human and economic cost related to fractures, the complications of the disease. Like other chronic disease, particularly silent diseases before complication, persistence to treatment is low. The approach is original and the methodology strong. The presentation is clear. The questions are well defined. The discussion and conclusion are well supported by the data. The manuscript is well written. The authors clearly show that the human (death) and economic importance develop new approach to improve persistence to oral bisphosphonate, the most used therapy in osteoporosis.

Thank you for those positive comments.

No major revision

**Comment:** The only minor comment is to review the labeling of figure and table in the text (particularly figure 1 and table 1) that doesn’t fit to the tables and the figure (Minor essential revision).

**Numbers on Figures and Tables** have been harmonized and a labeling on Table 1 was added.

**Level of interest:** An article of importance in its field  
**Quality of written English:** Acceptable  
**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.  
**Declaration of competing interests:**  
I declare that I have no competing interests
Date: 3 April 2011

Reviewer's report:

General comments

Compliance is a great concern in the field of chronic diseases. Particularly the extent of compliance concerns has been well demonstrated for osteoporosis. Consequently poor adherence is associated with decreased anti-fracture efficacy for bisphosphonates. In this context it is useful to assess the cost of non-persistence with oral bisphosphonates. Therefore the paper is of interest.

2 concerns should be raised however.

First, the authors used a Markov model that is usual. However by which mean this cohort was constituted is not clear. For example they indicated that with no treatment for a 10-year period and using a Monte-Carlo simulation the total number of fractures would be 20,401. The authors should clearly indicate by which mean they obtained this number.

Second, it seems that they used data extracted from PMSI source but this approach raises several concerns.

1- For vertebral fracture it is clear that the majority of vertebral fractures does not require a hospitalization. One estimates that only 10% of vertebral fractures requires to be hospitalized. Moreover for vertebral fractures, how the authors distinguished between osteoporotic fractures on one hand and traumatic or vertebral fractures due to malignancy in the other hand.

We agree with the reviewer that only a minority of vertebral fractures are hospitalized. The fact was taken into account in our model and clearly stated in the manuscript: “Morphometric (ie identified by radiography) and symptomatic (ie clinically diagnosed) vertebral fractures were differentiated.” (cf. Method – “Model structure” section) “Considering all vertebral fractures, only 23% were considered to be symptomatic [44] and were assumed to use medical resources. No cost/reward was given to other morphometric-defined vertebral fractures.” (cf. Method – “Costs” section).

Actually, we exclude from the cost analysis the fractures which were clearly not specific of osteoporosis (e.g. cervical, coccyx, etc.). Despite such cautions, we effectively could not differentiate fractures caused by trauma or malignant tumors from those due to osteoporosis. Nevertheless, whatever their original causes, we assumed that hospitalization costs of fractures were mainly dependent of their localization and management type.

This limitation was added in Discussion (cf. yellow).

2- The same remark can be done for wrist fractures. Indeed a high proportion of patients with wrist fractures are treated as outpatients.
As well, this limitation was added in Discussion (cf. yellow).

Specific comments

1- Introduction, p. 6 (2nd paragraph): The authors should indicate the strength of the present approach compared with previous studies done on this field.

A sentence has been added in Introduction (cf. yellow).

2- Methods, p. 8 (Figure 2): It is not clear why the authors did not use arrows indicating a possible relationship between for example both vertebral fractures and hip fractures and death.

In our model, death could end the simulation at any health states. No arrow was added on the Figure 1 in order to simplify the schema. As claimed in the text, excess of mortality in patient suffering a hip fracture or a vertebral fracture was applied according to published data [Error! Bookmark not defined., 29]. This model did not apply incremental mortality to the post-wrist fracture state as neither early nor medium term mortality has been shown [30].

3- Results, page 14, Table 2: Finally the overall cost for each fracture is? This point should be clearly explained.

Direct costs of management of each fracture site are presented in bold.

4- Results, page 17, Table 3: The number of clinical fracture for each category is slightly different from the number of fractured women. The authors should comment on this point.

The discrepancy is explained by the fact that several fractures could occurred to a same woman (cf. Results – “Simulation outcomes”: sentence in yellow)

5- Discussion, page 21: At the end of the page the authors indicate that monthly regimen would become the standard of oral bisphosphonates dosing frequency; I am not sure. Indeed the level of proofs for ibandronate in terms of prevention of hip fracture is not the same compared with others bisphosphonates. Secondly ibandronate will ne unreimbursed in France in 2011.

Actually, two molecules are now commercialized with monthly dosing. Ibandronate (80mg) was the first within the bisphosphonate class being proposed with a monthly regimen to post-menopausal women, recently followed by risedronate (75mg).

Seeing the quick and almost full switch of bisphosphonates with daily to weekly dosing regimen [Error! Bookmark not defined.] and data on better adherence with monthly dosing [39], we also assume the plausibility for monthly dosing regimen to become one day the standard of oral bisphosphonates dosing frequency.
As mentioned by the reviewer, in France, ibandronate is not reimbursed anymore (oral and IV formulations) because of a non proven efficacy at the hip site. This is actually not the case for risedronate monthly 75mg and in other countries but, as this paper is focus on French data, we added this important comment (cf. Discussion – in yellow).

6- Discussion, page 22: At the top of the page the authors claim that intravenous bisphosphonates in the field of osteoporosis could be practically restricted to niche of institutionalized patients; I am not sure that this sentence is really relevant.

We agree with the reviewer and the sentence has been changed for: “Those intravenous bisphosphonates may be particularly useful to treat patients with a high risk of non-persistence that could be simply identified by new validated tools, such as the recent ADEOS-12 items questionnaire [i]. Institutionalized patients may also easily benefit from those specific administration routes. However, experience has shown higher patient’s preference and acceptability for oral administration than for hospital infusion, for chemotherapy notably [ii].” (cf. Discussion – in yellow).

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**
I declare that I have no competing interests
This article aimed to estimate the cost of non-persistence with oral bisphosphonates (BP) in post-menopausal treatment in France. The article used a validated Markov model to estimate the cost of non-persistance in the French context.

The article is well-written, very well described (sometimes too much described..). The model is relevant, adapted to the study question. I have some discretionary revisions, which are described here:

1. Is the question posed by the authors well defined? yes this is clear

2. Are the methods appropriate and well described? The methods are well described and the hypothesis are justified and appropriate. This is correct. Page 15, the paragraph with begins by "Cost criterion" in the analyses section is written two times.

   The redundant sentence has been removed.

3. Are the data sound? yes, this is correct

4. Does the manuscript adhere to the relevant standards for reporting and data deposition? yes

5. Are the discussion and conclusions well balanced and adequately supported by the data?

The discussion section is too general in my opinion. There is insufficient discussion about the limitations of the model. For example, the authors could discuss the fact that direct medical cost of fractures were restricted to hospitalization (are all the fractures treated at hospital? Are some fractures managed in ambulatory sector?). In my opinion, cost is underestimated, as indirect cost, transport cost, and cost in ambulatory sector are not taken into account. This should be discussed.

   Those limitations are now stated as follow:
   “Several factors may contribute to a probable underestimation of the actual costs in this model. The majority of the vertebral fractures do not require hospitalization and were assumed as asymptomatic with no associated cost. However, many of those fractures probably lead to other ambulatory resource utilizations (e.g. back pain treatment). As well, due to the lack of data, cost estimations did not take in to account transport and indirect costs.”

Moreover, the authors should discuss the 10-years time horizon.
From a public health perspective, 10 years was assumed to be an appropriate time horizon in accordance with the one chosen for the FRAX® tool which has been developed by WHO to evaluate fracture risk of patients.

http://www.shef.ac.uk/FRAX/

“The FRAX® algorithms give the 10-year probability of fracture. The output is a 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture).”

6. Are limitations of the work clearly stated? see last response

7. Do the authors clearly acknowledge any work upon which they are building both published and unpublished? yes

8. Do the title and abstract accurately convey what has been found? yes

9. Is the writing acceptable? yes

Level of interest: An article of outstanding merit and interest in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I declare that I have no competing interests

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