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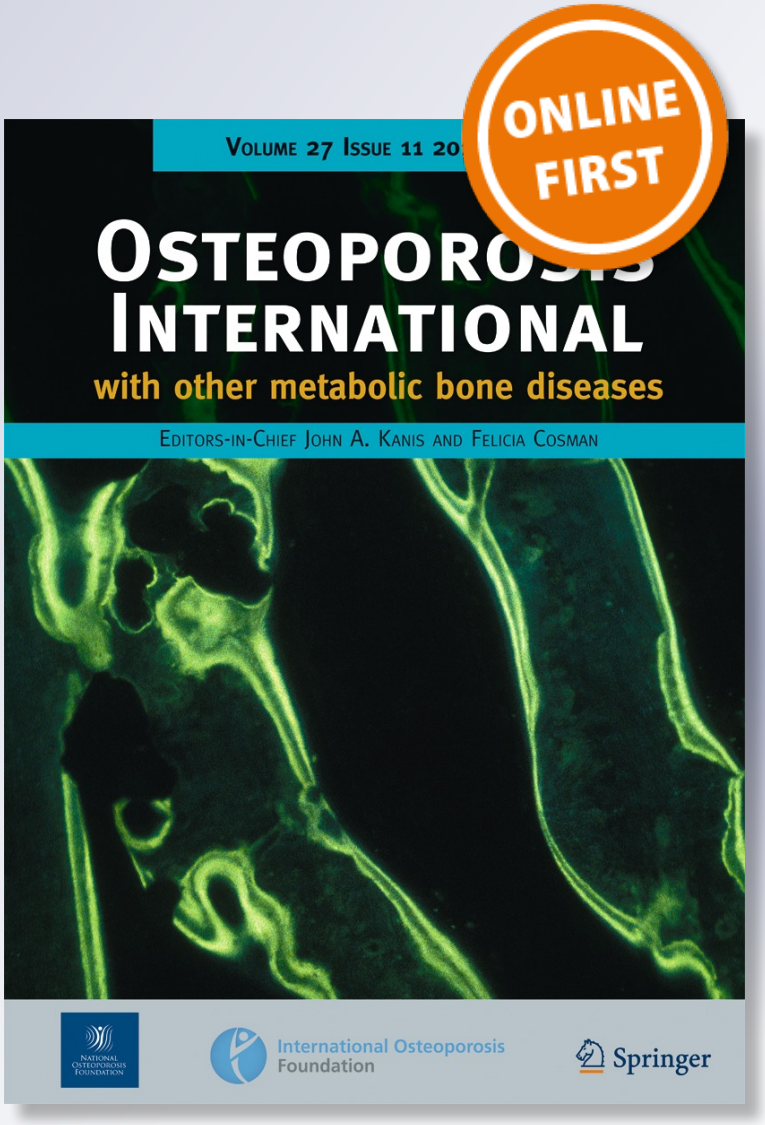

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ORIGINAL ARTICLE

Anti-osteoporotic treatments in France: initiation, persistence and switches over 6 years of follow-up

M. Belhassen[1,2,3] · **C. B. Confavreux**[4] · **B. Cortet**[5] · **L. Lamezec**[1] · **M. Ginoux**[2,3] · **E. Van Ganse**[2,3,6]

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Abstract
Summary Limited information is available on anti-osteoporotic treatment initiation patterns in France. In 2006–2013, the most frequently prescribed first-line treatment class for osteoporosis was represented by bisphosphonates (alendronic acid and risedronic acid), followed by strontium ranelate. Persistence with anti-osteoporotic treatment was low, with high proportions of treatment discontinuations and switches.
Introduction This epidemiological, longitudinal study described first-line treatment initiation, persistence, switches to second-line treatment, and medical care consumption in osteoporotic patients in France during the 2007–2013 period.
Methods Patients aged ≥50 years, who were recorded in a French claims database and did not die during the observation period, were included if they met ≥1 inclusion criteria for osteoporosis in 2007 (≥1 reimbursement for anti-osteoporotic treatment, hospitalisation for osteoporotic fracture (spine, hip, femur, forearm bones, humerus, wrist), or ≥1 reimbursement for long-term osteoporosis-associated status). We collected data on consumption of anti-osteoporotic treatment (alendronic acid, ibandronic acid, risedronic acid, zoledronic acid, raloxifene, strontium ranelate, teriparatide) and of osteoporosis-related medical care after the date of first reimbursement for anti-osteoporotic treatment.
Results We obtained 2219 patients with a 6-year follow-up and 1387 who initiated an anti-osteoporotic treatment in 2007 and who can be selected for the treatment regimen analysis. The most frequently used first-line treatments were alendronic acid (32.7 %), risedronic acid (22.4 %), strontium ranelate (19.3 %), ibandronic acid (13.1 %) and raloxifene (12.2 %). Among patients who received these treatments, the highest persistence after 6 years was observed for raloxifene (37.3 %), alendronic acid (35.1 %) and risedronic acid (32.3 %). Treatment discontinuations were reported for 35.5 % (raloxifene) to 53.4 % (strontium ranelate) and treatment switches for 27.4 % (alendronic acid) to 56.6 % (ibandronic acid) of these patients.
Conclusions This study showed that persistence with anti-osteoporotic treatment was relatively low in France, with high proportions of treatment discontinuations and switches, and that patients with osteoporosis were insufficiently monitored by bone specialists.

Keywords First-line treatment · France · Medical care · Osteoporosis · Persistence · Switch

✉ M. Belhassen
Manon.belhassen@univ-lyon1.fr

1 Merck Sharp and Dohme, Paris, France

2 PELyon, PharmacoEpidemiologie Lyon, Faculté d'Odontologie, 11 rue Guillaume Paradin, F-69372 Lyon, Cedex 08, France

3 HESPER 7425, Health Services and Performance Research, Claude Bernard Lyon 1 University, Lyon, France

4 INSERM UMR 1033—University of Lyon, Rheumatology Department, Edouard Herriot Hospital, Hospices Civils de Lyon, Lyon, France

5 Department of Rheumatology and EA 4490, Lille University Hospital, Lille, France

6 Respiratory Medicine, Croix-Rousse University Hospital, Lyon, France

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Introduction

Osteoporosis is characterised by a reduction in bone mineral density (BMD) and alterations of bone quality. Osteoporosis has been identified by the World Health Organisation (WHO) as a major public health concern due to its high prevalence and the serious consequences of osteoporotic fractures [1–3]. In France, the yearly number of osteoporotic fractures was estimated at nearly 380,000 in 2010 [4]. In a previous study, the overall prevalence of diagnosed osteoporosis in French women aged over 45 years was estimated at 9.7 % [5].

Diagnosis and intervention thresholds for osteoporosis are a major challenge. Currently, it relies on T-score assessed by BMD, fragility fracture or elevated hip or major osteoporotic fracture risk assessed by the FRAX tool [6–10]. The main objective of anti-osteoporotic therapies is to prevent fractures [3, 11, 12]. Bisphosphonates, including alendronic acid, ibandronic acid, risedronic acid and zoledronic acid, are the most frequently used anti-osteoporotic treatments [13–15]. Other classes of drugs are also available in France, such as selective oestrogen receptor modulators (raloxifene), strontium ranelate, parathyroid hormone analogue (teriparatide) or monoclonal antibodies (denosumab) [16]. Although effective treatments for osteoporosis are available, the number of fractures continued to increase in France between 2011 and 2013 [17]. In addition, patients who are candidates for anti-osteoporotic therapy should also be counselled about risk factor reduction, including the importance of calcium and vitamin D, exercise programs and cessation of tobacco use and alcohol abuse [12, 18, 19].

Limited information is currently available about anti-osteoporotic treatment initiation patterns among patients diagnosed with osteoporosis in France. Thus, we decided to conduct an epidemiological, longitudinal and retrospective study using data from the generalist sample of beneficiaries (EGB) in France, which is described in more detail below, to evaluate first-line anti-osteoporotic treatment initiation and persistence, switches to second-line treatment and consumption of osteoporosis-related medical care in patients who received a first anti-osteoporotic treatment between 2007 and 2013.

Methods

Description of EGB data source

Patients treated for osteoporosis were identified within the EGB database of the National Health Insurance Cross-Schemes Information System, which is a permanent representative sample of the population covered by French Health Insurance. The EGB contains anonymous information on socio-demographic and medical characteristics of health insurance beneficiaries, as well as the benefits they have received.

The EGB is based on a survey at the 97th percentile on the social security number (NIR) of French health insurance beneficiaries, whether they have received healthcare reimbursements or not [20]. By extrapolating, we estimated that an observation per 1000 individuals in the EGB reflects 97,000 patients. This database includes information on prescriptions but not on diagnoses, except when the long-term disease status is indicated or in the case of hospitalisation, as these are associated with the International Classification of Diseases, 10th edition (ICD-10) diagnosis codes filled by French hospitals. The database does not contain information on emergency room visits.

Since the EGB random selection method is based on individual NIRs, which remain the same throughout the entire life of patients, this database can easily be used to conduct longitudinal studies and to monitor treatment plans for various cohorts of EGB beneficiaries [21].

Study population

This study included patients aged 50 years or more, who were covered by the French Health Insurance between 2007 and 2013 (i.e. the period with available data from the EGB) and did not die during this period. Patients were included if they met at least one of the following criteria for osteoporosis in 2007: (i) at least one reimbursement for an anti-osteoporotic treatment, (ii) a hospitalisation for an osteoporotic fracture (spine, hip, femur, forearm bones, humerus, wrist) or (iii) at least one reimbursement for a long-term disease associated with an osteoporosis diagnosis.

Patients were excluded from the analysis if during the 12-month period before enrolment, they were hospitalised for Paget's disease or for a malignant tumour or if they had a declaration of long-term disease status for one of these conditions. Patients were also excluded if within the 12 months preceding the initial drug delivery, they had any osteoporosis-related claim.

In France, long-term disease status is specific for patients suffering from severe chronic conditions requiring expensive, long-term therapy. For these patients, the national healthcare system directly pays 100 % of all healthcare expenses related to the specific long-term disease, thus avoiding any co-payment.

In our study, we identified all eligible patients who received a first anti-osteoporotic treatment during the 6 years of observation period. The index date (year n) was defined as the date of the first reimbursement of an anti-osteoporotic treatment.

Data collection

For each patient, we collected all pertinent information about consumption of anti-osteoporotic therapy and related medical care from the index date until the end of the observational period.

We gathered information on delivery of the following anti-osteoporotic treatment classes: bisphosphonates (alendronic acid, ibandronic acid, risedronic acid and zoledronic acid), raloxifene, strontium ranelate and teriparatide.

In order to collect information about osteoporosis-related, non-drug therapy consumption, the following characteristics were identified in the EGB database: visits to public health professionals (rheumatologists, orthopaedic and traumatologic surgeons; general practitioners (GPs); and dentists), interventions from public health professionals (nurses, physiotherapists), bone densitometry measurements, orthopaedic reductions (fractures of the humerus, forearm bones or femur or total hip replacement), radiographs (spine, upper limb and lower limb), hospitalisations for or related to osteoporosis and consumption of supplements (calcium, vitamin D and analogues and calcium associated with vitamin D).

Analyses

We conducted a longitudinal persistence analysis over the 6 years of follow-up. Quantitative variables were described using descriptive statistics (medians, means and SDs) and qualitative variables with counts and percentages.

The analyses of persistence with first-line treatment, of treatment discontinuation and switches to second-line treatment were performed. A patient with treatment discontinuation was defined as a patient who stopped his first-line treatment during the 6-year follow-up period and did not switch to any other second-line treatment. The definition of discontinuation was the absence of dispensation of anti-osteoporotic treatment recorded in the year n + 1, with no new treatment (no switch). A patient with a treatment switch was defined as a patient who initiated a first-line treatment in 2007 and switched to another treatment during the 6-year follow-up period. The analysis of osteoporosis-related medical care consumption was also performed on all patients.

Statistical analyses were performed using the Statistical Analysis System (SAS)® software, version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Population

From the 379,970 patients covered by the French Health Insurance during the 2006–2013 period, 19,385 met at least one inclusion criteria for osteoporosis. Of these, 17,026 patients were ≥50 years of age; 2219 patients had a 6-year follow-up and were included in the analysis; among them 1387 patients received a first anti-osteoporotic treatment in 2007 and were included in the analysis of treatment regimens (Fig. 1).

First-line treatment initiation

Among the 1387 patients included in the analysis of treatment regimen, the two most frequently used first-line treatments were bisphosphonates (alendronic acid (32.7 %) and risedronic acid (22.4 %)), and the third one was strontium ranelate (19.3 %) (Table 1). While ibandronic acid (13.1 %) and raloxifene (12.2 %) were also frequently prescribed as first-line treatment, only four patients received teriparatide (0.3 %). Zoledronic acid, which was only reimbursed after December 2007 [21], was only prescribed to one patient (0.1 %).

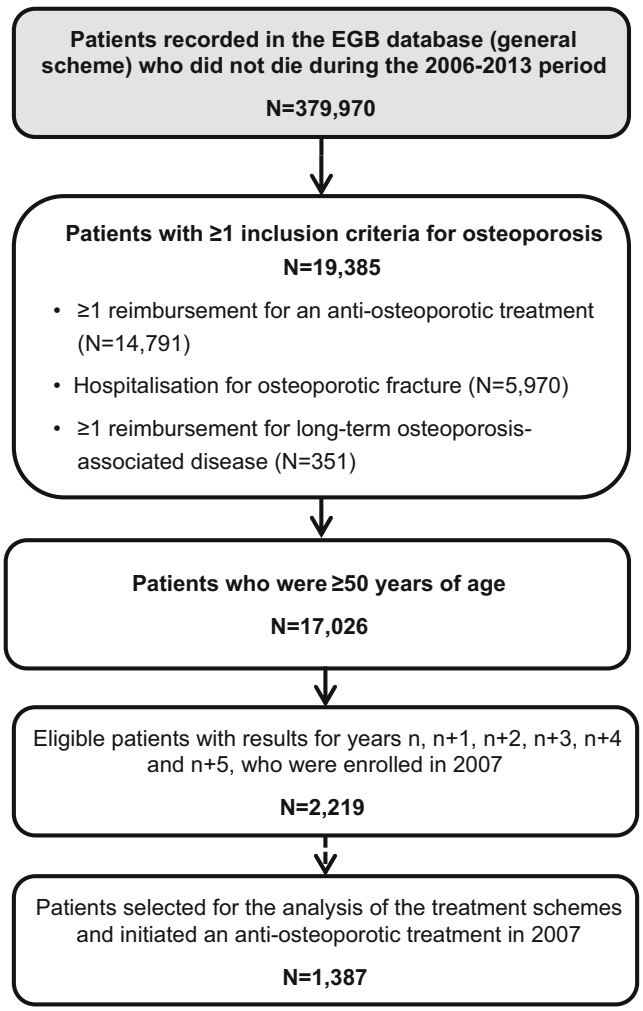

Fig. 1 Participant flow. *Footnote*: *year n* year of the treatment initiation; *N* number of patients

Table 1 Persistence with first-line treatment in patients enrolled in 2007, who were followed-up for 6 years after treatment initiation (n = 1387)

First-line treatment	Initiation of first-line treatment in 2007 (n (%))[a]	Still on first-line treatment in 2008 (n (%))[b]	Still on first-line treatment in 2009 (n (%))[b]	Still on first-line treatment in 2010 (n (%))[b]	Still on first-line treatment in 2011 (n (%))[b]	Still on first-line treatment in 2012 (n (%))[b]
Bisphosphonates						
Alendronic acid	*453 (32.7 %)*	328 (72.4 %)	252 (55.6 %)	218 (48.1 %)	196 (43.3 %)	159 (35.1 %)
Ibandronic acid	*182 (13.1 %)*	148 (81.3 %)	117 (64.3 %)	92 (50.5 %)	76 (41.8 %)	0 (0.0 %)
Risedronic acid	*310 (22.4 %)*	236 (76.1 %)	176 (56.8 %)	152 (49.0 %)	131 (42.3 %)	100 (32.3 %)
Zoledronic acid	*1 (0.1 %)*	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Raloxifene	*169 (12.2 %)*	120 (71.0 %)	96 (56.8 %)	86 (50.9 %)	77 (45.6 %)	63 (37.3 %)
Strontium ranelate	*268 (19.3 %)*	146 (54.5 %)	107 (39.9 %)	87 (32.5 %)	69 (25.7 %)	23 (8.6 %)
Teriparatide	*4 (0.3 %)*	3 (75.0 %)	2 (50.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0 %)

Classes set to italics indicate osteoporosis treatments

n total number of patients included in the analysis of treatment regimens, *n (%)* number (percentage) of participants who received the specific first-line treatment at each time point

[a] Percentage of the total number of patients included in the analysis (n = 1387)

[b] Percentage of patients who initiated the specific first-line treatment in 2007

During the 6-year follow-up, the proportion of consumers of vitamin D and analogues increased (from 12.3 to 42.1 %) while a decrease was observed in the proportions of consumers of calcium (from 8.7 to 4.4 %) or calcium associated with vitamin D (from 48.3 to 28.9 %) (Table 2).

Treatment persistence during the follow-up period

The proportion of patients who remained on first-line treatment after 6 years of follow-up ranged from 0.0 % (ibandronic acid, zoledronic acid and teriparatide) to 37.3 % (raloxifene) (Table 1).

Among patients receiving alendronic acid and risedronic acid, respectively, 159/453 (35.1 %) and 100/310 (32.3 %) remained on first-line therapy after 6 years of follow-up (Table 1). Moreover, 177/453 (39.1 %) and 130/310 (41.9 %) patients discontinued their first-line treatment with alendronic acid and risedronic acid without any switch (Table 3).

Among the 268 patients initially treated with strontium ranelate, only 23 (8.6 %) remained on first-line therapy after 6 years (Table 1) and 143 (53.4 %) discontinued their treatment without any switch (Table 3).

While 182 (13.1 %) patients took ibandronic acid during the first year of treatment, none of them persisted with this drug after 6 years of follow-up (Table 1), and 79 (43.4 %) discontinued their treatment without any switch (Table 3). Of note, 76/182 (41.8 %) patients stopped their first-line treatment with ibandronic acid during the last year of follow-up (Table 1).

Among the 169 patients who received raloxifene as first-line treatment, 63 (37.3 %) persisted with this drug during the six-year follow-up period (Table 1), and 60 (35.5 %) discontinued their treatment without any switch (Table 3).

Among the five most frequently used anti-osteoporotic drugs, the median duration of therapy before treatment discontinuation without any switch was the highest for ibandronic acid (1.9 years) and the lowest for strontium ranelate (0.8 years) (Table 3).

Treatment switches

While the highest proportion of treatment switches was observed in patients who received ibandronic acid as first-line-treatment, the longest median delay before treatment switch (4.3 years) was also observed in this group of patients (Table 3). Among the 103 patients initially treated with ibandronic acid and for whom a treatment switch was reported, most of them (77–74.1 %) went on bisphosphonates as second-line treatment either by alendronic acid (47 (45.6 %)) or risedronic acid (30 (29.1 %)).

A treatment switch was observed in 106/268 (39.6 %) patients initially treated with strontium ranelate and in 61/169 (36.1 %) patients initially treated with raloxifene. The most frequently prescribed second-line treatments were alendronic acid and risedronic acid with equal frequency: 34.9 % each after strontium ranelate and 27.9 % each after raloxifene.

A treatment switch was reported in 124/453 (27.4 %) patients initially treated with alendronic acid, with 39 (31.5 %)

Table 2 Osteoporosis-related, non-drug therapy consumption reported in patients enrolled in 2007, who were followed-up for 6 years after enrolment (n = 2219)

Medical services or supplements	Year n		Year n + 1		Year n + 2		Year n + 3		Year n + 4		Year n + 5	
	Number of consumers (%)	Mean number of medical services or boxes/ consumer (SD)	Number of consumers (%)	Mean number of medical services or boxes/ consumer (SD)	Number of consumers (%)	Mean number of medical services or boxes consumer (SD)	Number of consumers (%)	Mean number of medical services or boxes/ consumer (SD)	Number of consumers (%)	Mean number of medical services or boxes/ consumer (SD)	Number of consumers (%)	Mean number of medical services or boxes/ consumer (SD)
Consultations and visits to public health professionals (liberal)												
Rheumatologist	407 (18.3 %)	2.2 (2.1)	275 (12.4 %)	2.2 (2.1)	249 (11.2 %)	2.1 (1.9)	266 (12.0 %)	2.0 (1.9)	283 (12.8 %)	2.0 (1.9)	230 (10.4 %)	1.9 (1.3)
Orthopaedic and traumatologic surgeon	257 (11.6 %)	2.4 (1.5)	159 (7.2 %)	2.2 (1.7)	153 (6.9 %)	2.1 (1.5)	166 (7.5 %)	2.0 (1.4)	163 (7.3 %)	2.3 (2.5)	152 (6.8 %)	2.0 (1.2)
General practitioner	2123 (95.7 %)	8.8 (6.4)	2114 (95.3 %)	8.2 (6.2)	2098 (94.5 %)	8.2 (6.6)	2089 (94.1 %)	8.2 (6.7)	2079 (93.7 %)	8.2 (6.7)	2052 (92.5 %)	8.2 (6.2)
Dentist	303 (13.7 %)	1.3 (0.7)	338 (15.2 %)	1.2 (0.6)	324 (14.6 %)	1.2 (0.5)	319 (14.4 %)	1.3 (0.8)	333 (15.0 %)	1.3 (0.6)	327 (14.7 %)	1.2 (0.5)
Interventions from public health professionals (liberal)												
Nurse	653 (29.4 %)	47.0 (136.2)	63 (2.8 %)	30.6 (118.2)	56 (2.5 %)	42.5 (156.2)	55 (2.5 %)	60.4 (198.8)	466 (21.0 %)	68.3 (153.3)	976 (44.0 %)	127.4 (309.6)
Physiotherapists	644 (29.0 %)	24.5 (24.9)	3 (0.1 %)	34.7 (22.5)	3 (0.1 %)	17.7 (19.9)	7 (0.3 %)	24.3 (28.5)	352 (15.9 %)	21.0 (22.9)	723 (32.6 %)	38.8 (49.7)
Bone densitometry	212 (9.6 %)	1.0 (0.2)	153 (6.9 %)	1.0 (0.1)	143 (6.4 %)	1.0 (0.1)	182 (8.2 %)	1.0 (0.0)	169 (7.6 %)	1.0 (0.1)	158 (7.1 %)	1.0 (0.0)
Orthopaedic reduction	31 (1.4 %)	1.1 (0.2)	6 (0.3 %)	1.0 (0.0)	5 (0.2 %)	1.0 (0.0)	5 (0.2 %)	1.0 (0.0)	2 (0.1 %)	1.0 (0.0)	11 (0.5 %)	1.1 (0.3)
Humerus fracture	1 (<0.1 %)	1.0 (0.0)	0 (0.0 %)	0 (0)	0 (0.0 %)	0 (0)	0 (0.0 %)	0 (0)	0 (0.0 %)	0 (0)	0 (0.0 %)	0 (0)
Fracture of the forearm bones	12 (0.5 %)	1 (0)	0 (0.0 %)	0 (0)	0 (0.0 %)	0 (0)	1 (<0.1 %)	1 (0)	1 (<0.1 %)	1 (0)	0 (0.0 %)	0 (0)
Femur fracture	6 (0.3 %)	1 (0)	2 (0.1 %)	1 (0)	0 (0.0 %)	0 (0)	0 (0.0 %)	0 (0)	0 (0.0 %)	0 (0)	2 (0.1 %)	1 (0)
Total hip replacement	14 (0.6 %)	1 (0)	4 (0.2 %)	1 (0)	5 (0.2 %)	1 (0)	4 (0.2 %)	1 (0)	1 (<0.1 %)	1 (0)	10 (0.5 %)	1 (0)
Radiography	922 (41.6 %)	2.8 (1.9)	652 (29.4 %)	2.5 (2.0)	599 (27.0 %)	2.6 (1.8)	600 (27.0 %)	2.5 (1.8)	568 (25.6 %)	2.5 (1.8)	559 (25.2 %)	2.4 (1.8)
Spine	263 (11.9 %)	1.2 (0.6)	182 (8.2 %)	1.1 (0.4)	201 (9.1 %)	1.1 (0.3)	180 (8.1 %)	1.1 (0.4)	187 (8.4 %)	1.1 (0.3)	188 (8.5 %)	1.1 (0.4)
Upper limb	374 (16.9 %)	2.2 (1.6)	223 (10.0 %)	1.8 (1.3)	180 (8.1 %)	1.8 (1.2)	187 (8.4 %)	1.6 (0.8)	175 (7.9 %)	1.9 (1.2)	167 (7.5 %)	1.6 (1.0)
Lower limb	616 (27.8 %)	2.3 (1.7)	496 (22.4 %)	2.1 (1.8)	465 (21.0 %)	2.1 (1.6)	467 (21.0 %)	2.1 (1.5)	442 (19.9 %)	2.1 (1.4)	418 (18.8 %)	2.1 (1.6)
Hospitalisation for or related to osteoporosis	452 (20.4 %)	1.1 (0.4)	49 (2.2 %)	1.1 (0.3)	35 (1.6 %)	1.1 (0.4)	55 (2.5 %)	1.2 (0.5)	63 (2.8 %)	1.1 (0.3)	60 (2.7 %)	1.1 (0.3)
Supplements												
Calcium	192 (8.7 %)	5.0 (6.0)	136 (6.1 %)	5.5 (6.7)	145 (6.5 %)	5.6 (8.2)	137 (6.2 %)	6.5 (8.2)	131 (5.9 %)	5.5 (5.7)	97 (4.4 %)	5.6 (4.4)
Vitamin D and analogues	272 (12.3 %)	2.1 (1.5)	330 (14.9 %)	2.5 (1.9)	487 (21.9 %)	2.9 (2.2)	692 (31.2 %)	3.3 (2.3)	806 (36.3 %)	3.4 (2.4)	934 (42.1 %)	3.8 (2.7)
Calcium associated with vitamin D	1071 (48.3 %)	5.7 (3.9)	797 (35.9 %)	5.4 (3.6)	771 (34.7 %)	5.4 (3.6)	710 (32.0 %)	5.4 (3.6)	694 (31.3 %)	5.3 (3.6)	642 (28.9 %)	5.4 (3.7)

Classes set to italics indicate medical resources utilization

SD standard deviation, *year n* year of the treatment initiation, *n* total number of patients included in the analysis, % percentage of the total number of patients included in the analysis

Table 3 Analysis of treatment discontinuation and first-line switch in patients enrolled in 2007, who were followed-up for six years after treatment initiation (n = 1387)

First-line treatment n (%)[a]	Treatment discontinuation				Second-line treatment						
	Discontinuation without any switch n (%)[b]	Median duration before discontinuation (years)	Treatment switch n (%)[b]	Median duration before the switch (years)	Alendronic acid n (%)[b]	Ibandronic acid n (%)[b]	Risedronic acid n (%)[b]	Zoledronic acid n (%)[b]	Raloxifene n (%)[b]	Strontium ranelate n (%)[b]	Teriparatide n (%)[b]
Bisphosphonates											
Alendronic acid 453 (32.7 %)	177 (39.1 %)	1.0	124 (27.4 %)	1.3	–	39 (8.6 %)	28 (6.2 %)	15 (3.3 %)	9 (2.0 %)	31 (6.8 %)	2 (0.4 %)
Ibandronic acid 182 (13.1 %)	79 (43.4 %)	1.9	103 (56.6 %)	4.3	47 (25.8 %)	–	30 (16.5 %)	10 (5.5 %)	4 (2.2 %)	12 (6.6 %)	0 (0.0 %)
Risedronic acid 310 (22.4 %)	130 (41.9 %)	1.2	86 (27.7 %)	1.8	28 (9.0 %)	24 (7.7 %)	–	10 (3.2 %)	7 (2.3 %)	17 (5.5 %)	0 (0.0 %)
Zoledronic acid 1 (0.1 %)	1 (100 %)	0	0 (0.0 %)	0	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	–	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Raloxifene 169 (12.2 %)	60 (35.5 %)	1.2	61 (36.1 %)	2.9	17 (10.1 %)	10 (5.9 %)	17 (10.1 %)	1 (0.6 %)	–	16 (9.5 %)	0 (0.0 %)
Strontium ranelate 268 (19.3 %)	143 (53.4 %)	0.8	106 (39.6 %)	1.0	37 (13.8 %)	14 (5.2 %)	37 (13.8 %)	5 (1.9 %)	11 (4.1 %)	–	2 (0.7 %)
Teriparatide 4 (0.3 %)	0 (0.0 %)	0	4 (100 %)	1.4	1 (25.0 %)	0 (0.0 %)	3 (75.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	–

A patient with treatment discontinuation was defined as a patient who stopped first-line treatment during the six-year follow-up period and did not switch to any other second-line treatment. A patient with a treatment switch was defined as a patient who initiated a first-line treatment in 2007, and switched to another treatment during the six-year follow-up

n total number of patients included in the analysis of treatment regimens, *n (%)* number (percentage) of participants in the specified category

[a] Percentage of the total number of patients included in the analysis (n = 1387)

[b] Percentage of patients who initiated the specific first-line treatment in 2007

switches to ibandronic acid, 31 (25.0 %) to strontium ranelate and 28 (22.6 %) to risedronic acid. Among patients initially treated with risedronic acid, a treatment switch was reported for 86/310 (27.7 %) patients; 28 (32.6 %) switched to alendronic acid, 24 (27.9 %) to ibandronic acid and 17 (19.8 %) to strontium ranelate.

A treatment switch was observed in the four patients initially treated with teriparatide, with a median delay of 1.4 years before the switch. Three of these patients received risedronic acid as second-line treatment, and the last patient received alendronic acid.

Only one patient received zoledronic acid as first-line treatment, while 41 patients received it as second-line treatment.

Osteoporosis-related medical care and consumption of supplements in patients treated for osteoporosis

During the 6-year follow-up, the proportion of consultations with a rheumatologist or with an orthopaedic and traumatologic surgeon seemed to slightly decrease among osteoporosis patients, while the proportions of visits to GPs or dentists remained stable (Table 2). Of note, the proportions of patients who consulted a rheumatologist (range: 10.4 %–18.3 %) or an orthopaedic and traumatologic surgeon (range 6.8–11.6 %), or underwent bone densitometry (range 6.4–9.6 %) remained low throughout the study. In contrast, the proportion of interventions from nurses or physiotherapists increased during the follow-up period (Table 2).

The proportions of patients with orthopaedic reduction of a fracture of the humerus, forearm bones or femur, with total hip replacement or with radiography of the spine or the upper or lower limb tended to decrease during the first year following treatment initiation but remained stable in the subsequent years. Finally, the proportion of patients with a hospitalisation due to or related to osteoporosis was high during the first year after treatment initiation (20.4 %) but decreased during the subsequent years (≤2.8 %).

Discussion

This longitudinal study showed that the most frequently prescribed first-line treatment class for osteoporosis in France between 2007 and 2013 was bisphosphonates. At the individual drug level, the most frequently used treatments in 2007 were alendronic acid, risedronic acid and strontium ranelate. During the 6-year follow-up, the vast majority of patients discontinued their treatment without any switch or switched to a second-line treatment. This low persistence rate suggested that first-line treatments are often inappropriate in patients at high-risk for osteoporosis, with possibly little understanding by patients of the usefulness of the treatment. Treatment discontinuation could also be linked to safety concerns. For the vast majority of these high-risk patients, no consultations with a rheumatologist or BMD assessment were reported in the EGB database during the study period. These are signals of inadequate care to osteoporotic patients.

In our study, only approximately one third of patients treated with alendronic acid and risedronic acid persisted on first-line treatment during the 6-year follow-up period. Similar findings were obtained for ibandronic acid during the first 5 years of the follow-up, with 41.8 % of patients still on first-line treatment. However, no patients were treated with ibandronic acid during the last year of the follow-up, which may be explained by the fact that this drug has not been reimbursed anymore since December 2011. This change in reimbursement policies, together with the fact that ibandronic acid is only prescribed to patients at low risk for peripheral fractures, may also explain the high number of switches observed among patients who received this drug as first-line treatment [3]. The fourth bisphosphonate that was evaluated in our study was zoledronic acid, which was the only anti-osteoporotic treatment that seemed more frequently prescribed as second-line treatment than as first-line treatment. This observation is not surprising as the reimbursement of zoledronic acid started in December 2007 [22]; therefore, only one patient who received this drug as first-line treatment was included in the 6-year follow-up.

Persistence was also low (8.6 % after six years of follow-up) for first-line treatment with strontium ranelate, which has not been anymore reimbursed since March 2015. Even if the reimbursement policy only changed after the study, the prescription rate of strontium ranelate was affected by the warning for Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) released by the European Medicines Agency (EMA) in November 2007 [23] and the high media coverage associated with this warning [24]. In contrast, the consumption of teriparatide remained stable, although very low, during the 6-year follow-up. The low use of teriparatide may be explained by the constraints of this treatment (daily subcutaneous injection) and by the fact that first-line teriparatide therapy is only used and reimbursed in patients with at least two prevalent vertebral fractures [3]. Nevertheless, our results suggested that the persistence with teriparatide treatment was good in the few patients who used it, since the median treatment duration was close to 18 months, which corresponds to the complete reimbursed treatment sequence [3]. As expected, the four patients on first-line treatment with teriparatide switched to bisphosphonates (three to risedronic acid and one to alendronic acid). The last anti-osteoporotic treatment evaluated in our study was raloxifene (selective oestrogen receptor modulators), which was used as first-line treatment by 12.2 % of patients. A similar persistence rate, but with a higher proportion of switches, was observed in patients who received raloxifene as first-line treatment than in those treated with alendronic acid and risedronic acid. A potential explanation for this observation is the fact that raloxifene is reserved for use in patients at low risk for peripheral fractures [3].

Although persistence with anti-osteoporotic treatment was low in our study, it was higher than in a previous prospective study conducted in France in 2007, where the highest proportion of patients still on treatment after 1 year was around 50 % [24]. Another study also reported poor adherence and persistence with anti-osteoporotic medications, mostly in men, elderly, patients with glucocorticoid-induced osteoporosis and renal impairment; high-risk patients not well-controlled despite therapy and patients with pre-existing gastrointestinal conditions [25]. Persistence with anti-osteoporotic treatments in France should be improved since it is an important determinant of long-term outcomes [26–29], and it has a high economic impact [30–32]. A previous study conducted in France showed that intermittent regimens were associated with higher persistence rates, but this was not evaluated in our analysis [24]. Results on persistence rates could be also impacted by the definition of discontinuation. In a recent literature review, Karlsson and colleagues [33] identified 40 retrospective studies reporting at least one estimate of 12- or 24-month persistence with oral BPs, using varying methodologies. While all studies were similar in terms of how persistence was defined, they varied in the size of the permissible gap, which is directly related to the probability of being defined as non-persistent. The pooled estimate from the literature review showed that 45 % of patients were persistent with oral BP therapy after 12 months, which is in line with our study.

North American studies had a slightly lower pooled estimate of 12-month persistence compared with European studies (43 vs. 46 %) [33]. In the literature, estimates of 12-month persistence varied widely, from 10 to 78 %, with the majority of estimates ranging from 30 to 60 % [33]. In Sweden, 12-month persistence with oral BPs was reported to be 51 % [34] and 52 % (in patients starting treatment in 2009) or 67 % (in those starting treatment in 2006) [35]. Studies investigating the differences between daily and weekly oral BPs reported that daily administration was associated with lower 12-month persistence compared with weekly administration (pooled estimates: 36 vs. 48 %, respectively) [33].

Other factors may impact the treatment persistence, such as hospitalisation for osteoporosis, initial prescription of treatment by a rheumatologist or BMD assessments [35, 36]. In our study, the proportion of consultations with a rheumatologist were low during the 6-year follow-up, and the number of hospitalisations for or related to osteoporosis were high during the first year but low during the subsequent years of the follow-up. Since hospitalisations for fractures are often good opportunities to initiate anti-osteoporotic treatments, the higher number of hospitalisations during the first year may be explained by the inclusion and exclusion criteria in our study. Indeed, only patients who initiated treatment in 2007 were included, and those who were treated for osteoporosis, fractures or long-term diseases in 2006 were excluded. An alternative approach would have been to include all patients starting an osteoporotic treatment during any year. This approach would have indeed increased the sample size, but we wanted to focus on long-term follow-up where available data on persistence rates are scarce in literature.

Although BMD assessment is recommended and has been reimbursed since 2006 according to national guidelines in France [3], it was only assessed in a minority of patients in our study. This observation is in line with the findings of a previous study showing that only 10.0 % of women 50 years of age or older in France underwent BMD assessment after a forearm fracture [37]. BMD should be tested routinely in osteoporotic patients since a previous study has shown that persistence improved when BMD testing was carried out before the initial prescription and after 3–6 months of therapy [24]. Future studies are needed to further evaluate the interactions between these factors (BMD testing, visit to a rheumatologist, and hospitalisation for osteoporosis) and anti-osteoporotic treatment persistence.

The main strengths of this study are the relatively large sample size and the fact that the study population is representative of the French population. Limitations of this study included the lack of osteoporosis diagnosis in the EGB, and the fact that claims for anti-osteoporotic treatments do not indicate whether medications were consumed as prescribed or not. The EGB database is a claim database and thus could not capture the patients who received a prescription from a physician but did not buy it. A further limitation was the fact that not all anti-osteoporotic treatments were included in the analysis; for example, denosumab, which has been reimbursed since December 2011 as second-line treatment after at least 3 months of bisphosphonate therapy, could not be evaluated [38]. Since reasons of death are not recorded in the EGB database, we could not capture patients who specifically died from hip fracture and decided to exclude people who died during follow-up to ensure robust persistence rates.

In conclusion, this study confirms that persistence with anti-osteoporotic treatment is relatively low in France, with a high proportion of patients who either discontinued their treatment or switched to a second-line treatment. Our results also show that the proportions of consultations with rheumatologists and BMD assessments are low. These findings show that efforts are needed to optimise the management of patients treated for osteoporosis in order to improve their prognosis and stress the importance of raising awareness of the physicians who treat these patients (GPs, emergency physicians and surgeons). In France, the recommendations for the treatment of osteoporosis published in 2006 were updated in 2012 by the Groupe de Recherche et d'Information sur les Ostéoporoses (GRIO) and the French Society for Rheumatology, with the participation of several learned societies [3, 39]. The impact of the new recommendations on treatment persistence should be evaluated in future studies.

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Compliance with ethical standards

Conflicts of interest MB was a PhD student and part-time employee of MSD France at the time of the study. CBC received honorarium from Amgen, Lilly, MSD. BC received honorarium from Amgen, Ferring, Lilly, Medtronic, MSD, Roche diagnostics. LL is a full-time employee of MSD France. MG has nothing to declare. EVG has nothing to declare.

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