

Persistence with denosumab and persistence with oral bisphosphonates for the treatment of postmenopausal osteoporosis: a retrospective, observational study, and a meta-analysis

L. Karlsson¹ · J. Lundkvist³ · E. Psachoulia⁴ · M. Intorcchia⁴ · O. Ström^{1,2}

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Abstract

Summary The objectives of this study were to estimate persistence with denosumab and put these results in context by conducting a review of persistence with oral bisphosphonates. Persistence with denosumab was found to be higher than with oral bisphosphonates.

Purpose This study had two objectives: to analyse persistence in Swedish women initiating denosumab for treatment of postmenopausal osteoporosis (PMO) and to put these findings in context by conducting a literature review and meta-analysis of persistence data for oral bisphosphonates.

Methods The study used the Swedish Prescribed Drug Register and included women aged at least 50 years initiating denosumab between May 2010 and July 2012. One injection of denosumab was defined as 6-month persistence. Women were considered persistent for another 6 months if they filled their next prescription within 6 months+56 days and survival analysis applied to the data. A literature search was conducted in PubMed to identify retrospective studies of persistence with oral bisphosphonates and pooled persistence estimates were calculated using a random-effects model.

Results The study identified 2,315 women who were incident denosumab users. Mean age was 74 years and 61 % had been previously treated for PMO. At 12 and 24 months, persistence with denosumab was 83 % (95 % CI, 81–84 %) and 62 % (95 % CI, 60–65 %), respectively. The literature search identified 40 articles for inclusion in the meta-analysis. At 12 and 24 months, persistence with oral bisphosphonates ranged from 10 % to 78 % and from 16 % to 46 %, with pooled estimates of 45 % and 30 %, respectively.

Conclusion These data from the Swedish Prescribed Drug Register and literature review suggest that persistence was higher with denosumab than with oral bisphosphonates.

Keywords Bisphosphonates · Denosumab · Meta-analysis · Persistence · Retrospective · Review

Introduction

Osteoporosis is a disease characterized by excessive bone resorption leading to reduced bone strength and an increased risk of fracture. In women, reduced oestrogen levels during or after menopause can lead to postmenopausal osteoporosis (PMO) [1].

There are several treatments available for osteoporosis, which have the primary aim of reducing the risk of fracture [2, 3]. For optimal outcomes, patients need to take their treatment according to the dosing instructions and for the prescribed duration (i.e., they need to be both compliant and persistent with therapy) [4]. Studies in both the USA and Europe have shown that persistence with osteoporosis treatment is important for reducing the risk of fracture [5–7]. The data indicate that, compared with treatment lasting for less than 1-month, treatment must extend beyond 1 year in order to significantly reduce 3-year fracture incidence [6]. Evidence suggests, however, that approximately 50 % of women do not follow their prescribed osteoporosis treatment

✉ L. Karlsson
linda.karlsson@quantifyresearch.com

¹ Quantify Research, Hantverkargatan 8, SE-112
21 Stockholm, Sweden

² Department of Learning, Informatics, Management and Ethics (LIME), Medical Management Centrum (MMC), Karolinska Institutet, Stockholm, Sweden

³ Department of Pharmacy, Uppsala University, Uppsala, Sweden

⁴ Amgen (Europe) GmbH, Zug, Switzerland

regimen and 50 % discontinue treatment within 1 year [8, 9]. Hence, persistence is an important consideration in the overall management of patients with osteoporosis. Moreover, modelling studies have shown that the incorporation of persistence in health economic evaluations can have a considerable impact on the estimated cost-effectiveness of an intervention [10, 11].

Oral bisphosphonates (BPs), including both alendronate and risedronate, are the current mainstay of anti-osteoporosis treatment in Europe [12]. Oral BPs can be administered daily, weekly, or monthly. An alternative treatment option is denosumab, a fully human monoclonal antibody that inhibits the RANK ligand, which is administered as a 60-mg subcutaneous injection once every 6 months. Denosumab 60 mg is indicated for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fracture, and for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fracture [13]. Denosumab 60 mg has also been shown to increase bone mass in women with bone loss associated with adjuvant aromatase inhibitor therapy [14].

In patients with osteoporosis, the long-interval subcutaneous dosing regimen of denosumab could enable higher persistence with therapy than that observed with other anti-osteoporosis treatments [7, 9]. Indeed, levels of 12-month persistence have been reported with denosumab that vastly exceed the 50 % rate cited above. In a randomized, cross-over trial comparing denosumab with alendronate, 91 % of patients were persistent with treatment over 12 months, whilst in two single-arm, prospective, observational studies conducted in the USA, Canada, Austria, Belgium, Greece, and Germany, 12-month persistence rates varied from 82 to 94 % across countries [15–17]. To our knowledge, however, no study of real-world persistence with denosumab therapy in Sweden has yet been published.

This study had two objectives. The first was to estimate persistence in Swedish women in whom denosumab treatment was initiated for PMO and to explore patient characteristics that might affect persistence. The second was to put the findings regarding persistence with denosumab into context by conducting a literature review and meta-analysis of published, retrospective data on persistence with oral BPs.

Methods

Persistence with denosumab

Data source and patient selection

This study involved the analysis of data from the Swedish Prescribed Drug Register, which contains information on drugs dispensed on prescription since 2005 for the Swedish population (approximately 9.6 million individuals) [18]. Mortality data were collected from the Swedish Causes of Death Register, which includes death dates for all people residing in

Sweden at the time of death. Swedish national registers have a high degree of accuracy. The loss of patient information from the Swedish Prescribed Drug Register is less than 0.6 % of all possible values and fewer than 0.5 % of all deaths are missing from the Causes of Death Register [19].

Women aged 50 years or older in whom denosumab treatment was initiated between 1 May 2010 and 31 July 2012 were identified in the Swedish Prescribed Drug Register. To capture relevant baseline characteristics, data needed to be available for at least the 18-month period before treatment initiation (the pre-index period). Similarly, to accumulate sufficient follow-up time to study persistence, data needed to be available for at least the 8-month period immediately following treatment initiation. The analysis focused on women with PMO and included only those receiving denosumab 60 mg. As denosumab is also used to increase bone mass in patients with bone loss associated with adjuvant aromatase inhibitor therapy, patients filling prescriptions for aromatase inhibitors in the pre-index period were excluded from the study.

Definition of persistence

Persistence was defined as the number of days from the date of treatment initiation to the end of the duration of the last filled prescription or the end of the study period (31 March 2013). One injection of denosumab equated to 6 months' persistence; hence, all women were defined as being persistent with therapy for at least 6 months. Women were considered to be persistent for an additional 6 months if they filled their next denosumab prescription within 6 months+56 days of administration of the previous injection (i.e., a gap of 56 days was permitted) [4]. Women failing to refill their prescription before the end of the permissible gap were defined as being non-persistent 6 months after the last filled prescription.

Covariates

The covariates used in the analysis were: age; previous osteoporosis treatment in the pre-index period; glucocorticoid use, defined as filling a prescription for cortisone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone, betamethasone, or dexamethasone equivalent to at least 450 mg of prednisolone in the pre-index period [20]; concurrent calcium and/or vitamin D supplementation, defined as filling prescriptions corresponding to at least 109,500 mg of calcium (1,200 mg/day for 3 months) and/or 73,000 IU of vitamin D (800 IU/day for 3 months) in the 6 months after treatment was initiated [21]; dependency, defined as living in a dependent/institutionalized setting (determined on the basis of the initial prescription being pre-dispensed); and receiving primary care (defined as the initial prescription being prescribed in the primary care setting).

Statistical analyses

Persistence with therapy was estimated at 12, 18, and 24 months using Kaplan–Meier survival curves, with non-persistence as the failure event. Women were censored for death and end of data availability (31 March 2013). Covariates associated with non-persistence were investigated using a parametric proportional hazards model (Weibull distribution).

The effects of alternative permissible gaps of 30, 90, and 180 days were explored using sensitivity analyses. Denosumab has a biannual dosing regimen and women may refill their prescriptions several months earlier than the date on which the next injection is needed, which can result in long gaps between prescriptions. This possible accumulation of denosumab was accounted for in another sensitivity analysis, which used a 56-day permissible gap and permitted women to cover future gaps between filled prescriptions with previously dispensed medication.

Subgroup analyses were conducted according to the calendar year of the index denosumab injection. Further subgroup analyses compared persistence in treatment-naïve women with that in treatment-experienced women. The latter group was defined as those with a prescription for another anti-osteoporosis drug (alendronate, risedronate, ibandronate, etidronate, zoledronic acid, strontium ranelate, raloxifene, or parathyroid hormone analogue) in the pre-index period.

Model distribution and covariate selection were based on maximizing the log-likelihood and minimizing the Akaike information criterion. The proportional hazards assumption was tested by graphical inspection and by exploring whether the included covariates significantly varied over time. The statistical analysis was executed using Stata 12 (StataCorp LP, College Station, TX, USA).

Persistence with oral bisphosphonates

Literature review

The literature review focused on persistence with oral BPs, which are the most commonly used treatments for osteoporosis in Europe and the USA [1]. Retrospective studies that estimated treatment persistence with oral BPs at 12 and 24 months were identified in the PubMed database. The search string used was “osteoporo*[All fields] AND (persistence[All fields] OR adherence[All fields] OR compliance[All fields] OR discontin*[All fields]) AND (register*[All fields] OR claim*[All fields] OR record*[All fields] OR health plan*[All fields] OR pharmacy*[All fields] OR prescript*[All fields]) OR (osteoporosis[All fields] AND persistence[All fields])”. Searches also included the MeSH terms “patient compliance”, “compliance”, “postmenopausal”, and “osteoporosis”. The search

encompassed all articles published until 22 November 2013 with an English-language abstract.

In addition to the PubMed database search, seven review articles [22–28] were cited in the papers included after the literature search and full-text review. These review articles were manually searched to identify articles not found using the search string. To be included in this study, an article needed to present at least one estimate of 12- and 24-month persistence with oral BP treatment. No additional inclusion criteria were used.

Statistical analyses

Pooled estimates of persistence at 12 and 24 months were calculated using a random-effects model [29]. Subgroup analyses of 12-month persistence were conducted according to frequency of administration (weekly and daily; only for those studies directly comparing these two frequencies) and region (Europe, North America, and other).

Results

Persistence with denosumab

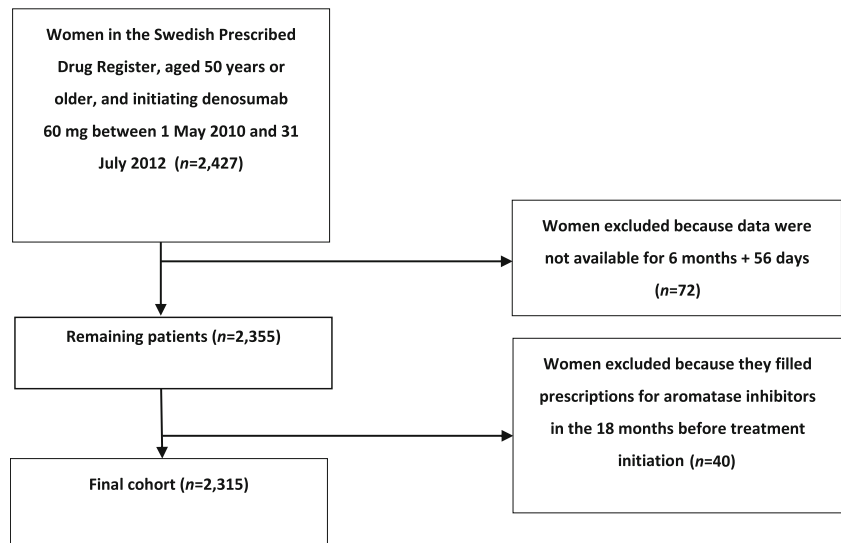
Study population

The final cohort consisted of 2,315 incident users of denosumab (Fig. 1) who contributed a total of 2,747 person-years. Baseline patient characteristics are presented in Table 1. Women were followed up for a mean (median) of 433 (387) days, until censoring or non-persistence with therapy. The majority (61 %) of women had received another anti-osteoporosis treatment in the 18 months before starting denosumab treatment. Approximately two fifths of women were prescribed their initial prescription medication in a primary care setting, and approximately one fifth had received glucocorticoids before initiation of denosumab treatment. Even though the inclusion period continued to 31 July 2012, the majority (62 %) of women filled their index prescription in 2010 or 2011.

Persistence

The estimated Kaplan–Meier curves for persistence with denosumab are presented in Fig. 2. Using a permissible gap of 56 days, persistence with denosumab treatment was 83 % (95 % CI, 81–84 %) at 12 months, 69 % (95 % CI, 67–71 %) at 18 months, and 62 % (95 % CI, 60–65 %) at 24 months. Increasing the permissible gap to 90 and 180 days, 12-month persistence was 84 % (95 % CI, 83–86 %) and 87 % (95 % CI, 86–88 %), respectively. Decreasing the permissible gap to 30 days, 12-month persistence was 78 % (95 % CI, 76–79 %).

Fig. 1 Flow chart of the selection of women with PMO initiating denosumab 60 mg



The sensitivity analysis allowing patients to have overlapping prescriptions showed results similar to the analysis with a permissible gap of 90 days (data not shown).

At 24 months, women who had received previous anti-osteoporosis treatment (during the pre-index period) were more likely to be persistent with therapy than those who had not (65 vs. 58 %, $p < 0.001$); no difference was observed at 12 months ($p = 1.000$). No difference in 12-month persistence

was found between women whose denosumab treatment was initiated in 2010 or 2011 and those first receiving denosumab in 2012 ($p = 1.000$).

Determinants of non-persistence

A multivariate Weibull model was fitted to identify variables that were significantly associated with non-persistence (Table 2). For all included covariates, no significant evidence of non-proportional hazards was observed (data not shown). Previous anti-osteoporosis treatment (during the pre-index period) was associated with a higher rate of persistence compared with no previous treatment. Filling a prescription for calcium and vitamin D supplementation in the first 6 months after denosumab initiation was also found to be associated with a higher persistence rate. Glucocorticoid treatment during the pre-index period was associated with a lower denosumab

Table 1 Baseline characteristics of women with PMO initiating denosumab 60 mg

Characteristic	Study population (N=2,315)
Follow-up, days ^a	433.4±183.3
Age, years ^b	73.7±9.0
Previous anti-osteoporosis treatment ^c	1,406 (60.7)
Glucocorticoid use ^d	483 (20.9)
Concurrent calcium/vitamin D supplementation ^e	826 (35.7)
Dependency/institutionalized ^f	98 (4.2)
Primary care ^g	903 (39.0)
Filling first prescription in 2010 or 2011	1,426 (61.6)
Filling first prescription in 2012	889 (38.4)

Data are mean±standard deviation or n (%)

^a Time until censoring or non-persistence

^b Age of patient at initiation of denosumab treatment

^c Experience of any other anti-osteoporosis treatment in the 18 months before initiation of denosumab treatment

^d Filling prescriptions equivalent to at least 450 mg of prednisolone in the 18 months before initiation of denosumab treatment

^e Filling prescription for calcium and vitamin D supplements in the 6 months after initiation of denosumab treatment

^f Receiving initial denosumab prescription as pre-dispensed

^g Initial denosumab prescription prescribed in the primary care setting

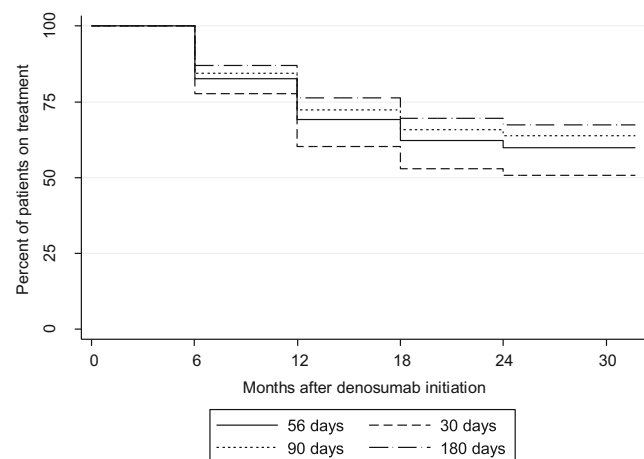


Fig. 2 Kaplan–Meier estimates of persistence with denosumab therapy for permissible gaps of different lengths

Table 2 Determinants of non-persistence with denosumab treatment (Weibull hazards model)

Covariate	Hazard ratio	95 % confidence interval	<i>p</i> value
Age	1.00	0.99–1.01	0.48
Previous anti-osteoporosis treatment ^a	0.85	0.73–0.98	0.03
Glucocorticoid use ^b	1.28	1.08–1.53	0.01
Concurrent calcium/vitamin D supplementation ^c	0.80	0.68–0.93	0.01
Dependency/institutionalized ^d	0.97	0.66–1.43	0.88
Primary care ^e	1.09	0.94–1.27	0.25

A hazard ratio >1 indicates a higher probability of discontinuing treatment relative to continuing treatment. Estimated model parameters: constant=0.20 and $p=1.49$

^a Experience of any other anti-osteoporosis treatment in the 18 months before initiation of denosumab treatment

^b Filling prescriptions equivalent to at least 450 mg of prednisolone in the 18 months before initiation of denosumab treatment

^c Filling prescriptions for calcium and/or vitamin D supplements in the 6 months after initiation of denosumab treatment

^d Receiving initial denosumab prescription as pre-dispensed

^e Initial denosumab prescription prescribed in the primary care setting

persistence rate. Age, pre-dispensing of the initial prescription, and receiving treatment in the primary care setting did not have significant effects on persistence levels.

Literature review and meta-analysis: persistence with oral bisphosphonates

Included articles

The search of the PubMed database identified 663 articles, most of which were excluded on the basis of their title or abstract (Fig. 3). The most frequent reasons for exclusion were: not reporting an estimate of 12- or 24-month persistence; discussing only hormone replacement therapy, osteoporotic fractures, or calcium/vitamin D supplementation; not using retrospective data; not having been written in English; and being a review. Review articles were manually searched for any articles that had not been identified by the search of PubMed [22, 28].

In total, 40 articles were included in the final review and meta-analysis (Table 3) [5, 6, 30–67]. These included studies from 12 different countries, with the largest number of studies being conducted in the USA (17 studies) [5, 35–38, 41, 42, 46, 49–51, 54, 56, 59, 63, 64, 66] and the next largest number being conducted in the Netherlands (four studies) [43, 44, 48, 61]. Two studies used the Swedish Prescribed Drug Register [6, 47]. In the majority of studies, a patient was defined as non-persistent with treatment if the time period between two

consecutive prescription fills exceeded the length of the permissible gap. The most commonly used permissible gap was 30 days [5, 30, 32–40, 44, 49, 52, 55, 56, 58, 61, 65]; other commonly used permissible gaps were 60 and 90 days. In nine studies [6, 31, 40–42, 45, 47, 64, 66], patients were allowed to accumulate medicine (i.e., use supply from a previous prescription) and in 16 studies [6, 30–32, 34, 39, 40, 44–46, 52, 54, 55, 57, 61, 63], they were allowed to switch between treatments during the study period (e.g., from alendronate to risedronate or from weekly to daily oral BPs). The studies varied in the type of data source used (e.g., claims, medical charts), type of patients included (e.g., women with PMO, treatment-naïve women), and type of oral BP prescribed (e.g., alendronate, risedronate).

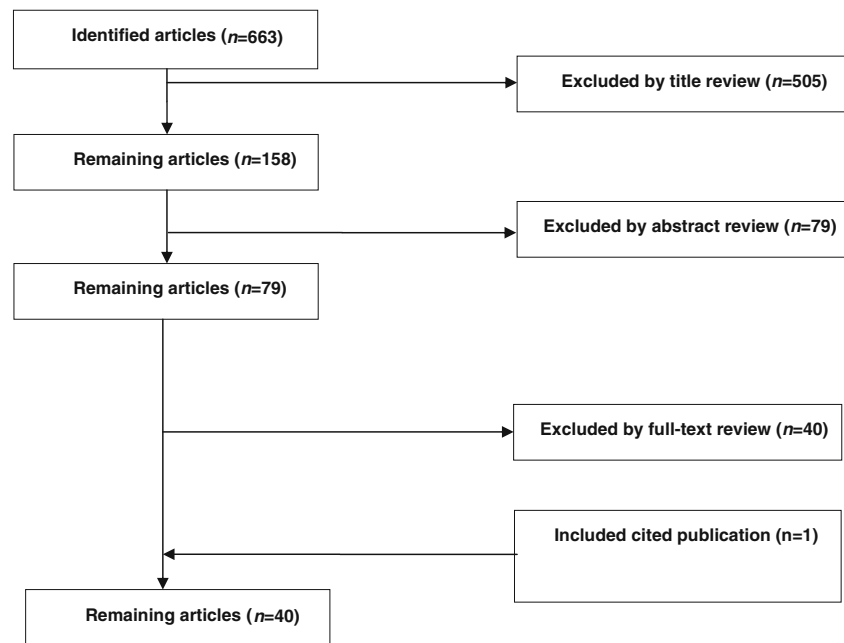
Persistence at 12 and 24 months

Of the 40 included studies, 39 reported at least one estimate of 12-month persistence with treatment (Fig. 4) [6, 30–67] and 17 [5, 6, 31, 32, 37, 45, 46, 48, 50–52, 55, 58, 59, 61, 64, 65] reported at least one estimate of 24-month persistence (Table 3). Estimates of 12-month persistence varied widely, from 10 to 78 %, with the majority of estimates ranging from 30 to 60 %, and there was a large amount of heterogeneity between studies in the methods used (Fig. 4). The pooled estimate of 12-month persistence with oral BP therapy was 45 % (95 % CI, 41–49 %). Estimates of 24-month persistence ranged from 16 to 46 % (Table 3), and the pooled estimate was 30 % (95 % CI, 25–35 %). In Sweden, 12-month persistence with oral BPs was reported to be 51 % [6], and 52 % (in patients starting treatment in 2009) or 67 % (in those starting treatment in 2006) [47], and 24-month persistence reported to be 25 % [6] (Table 3).

Studies investigating the differences between daily and weekly oral BPs [30, 35–37, 50, 55] reported that daily administration was associated with lower 12-month persistence compared with weekly administration (pooled estimates: 36 vs. 48 %, respectively) (Fig. 4). North American studies had a slightly lower pooled estimate of 12-month persistence compared with European studies (43 % based on 19 studies vs. 46 % based on 16 studies) (Fig. 4). The pooled 12-month estimate of persistence in other regions (based on four studies) was higher than the European and North American estimates. The results of studies varying the permissible gap all indicated that wider permissible gaps were associated with higher persistence with treatment [6, 31, 33, 41, 45, 49, 51, 63, 64, 66].

Discussion

For optimal clinical outcomes, women with PMO need to persist with anti-osteoporosis medications for the prescribed treatment duration. To the best of our knowledge, this is the

Fig. 3 Flow chart of the literature search**Table 3** Summary of data included in the literature review

Publication	Country	Number of women	Treatment for which persistence was assessed	Female (%)	Permissible gap	12/24-month persistence (%) ^b
Balasubramanian et al. (2013) [64]	USA	92,839	ALE-IBA-RIS-other	100	60 days	42/30
Brankin et al. (2006) [30]	UK	15,330	ALE-RIS	100	30 days	Weekly vs. daily GPRD: 52/- vs. 40/- MEDIPLUS: 44/- vs. 33/- DIN-LINK: 70/- vs. 56/-
Burden et al. (2012) [31]	Canada	451,113	ALE-ETI-RIS	84	60 days	63/46
Cheen et al. (2012) [32]	Singapore	798	ALE-RIS	92	30 days	69/18
Cheng et al. (2013) [58]	Taiwan	2,975	ALE-other	90	30 days	51/38
Chiu et al. (2013) [65]	Taiwan	333	ALE-other	0	30 days	46/30
Cotte et al. (2008) [34]	France	2,468	ALE-ETI-RIS-other	100	30 days	Previous fracture: 34/- No previous fracture: 41/-
Cotte et al. (2010) [33]	France	2,990	ALE-IBA-RIS	100	Monthly: 45 days Weekly: 30 days	Monthly: 48/- Weekly: 30/-
Cramer et al. (2005) [35]	USA	2,741	ALE-RIS	100	30 days	Weekly: 44/- Daily: 32/-
Cramer et al. (2006) [36]	USA	15,640	ALE-RIS	100	30 days	Weekly vs. daily USA: 44/- vs. 32/- UK: 52/- vs. 40/- France: 51/- vs. 44/-
Curtis et al. (2006) [59]	USA	1,158	ALE/RIS	77–80	90 days	ALE: 52/40 RIS: 50/40
Gallagher et al. (2008) [53]	UK	44,531	ALE-RIS	81	90 days	58/-
Gold et al. (2007) [37]	USA	4,769	ALE	100	30 days	Weekly: 36/24 Daily: 26/16
Gold et al. (2009) [54]	USA	263,383	IBA/RIS	93–94	90 days	IBA: 18/- RIS: 40/-
Hadji et al. (2012) [55]	Germany	4,147	ALE-ETI-IBA-RIS-other	100	30 days	28/13
Hansen et al. (2013) [57]	Denmark	100,556	Not specified	85	56 days	61/-
Huybrechts et al. (2006) [38]	USA	38,120	ALE-RIS-other	100	30 days	78/-

Table 3 (continued)

Publication	Country	Number of women	Treatment for which persistence was assessed	Female (%)	Permissible gap	12/24-month persistence (%) ^b
Jones et al. (2008) [39]	Canada	62,897	ALE/RIS	100	30 days	ALE: 56/ RIS: 54/–
Landfeldt et al. (2012) [6]	Sweden	56,586	ALE–RIS–other	86	56 days	51/25
Li et al. (2012) [40]	UK	66,116	ALE–ETI–IBA–RIS–other	100	30 days	32/–
Lo et al. (2006) [41]	USA	13,455	ALE	100	60 days	50/–
McCombs et al. (2004) [42]	USA	3,720	ALE–ETI–RIS	93	14 days	24/–
McGowan et al. (2013) [60]	Ireland	1,565	Not specified	Not reported	35 days	Urban: 46/ Rural: 50/–
Netelenbos et al. (2011) [43]	Netherlands	8,626	ALE–RIS–other	80	183 days	43/–
Penning-van Beest et al. (2006) [44]	Netherlands	2,124	ALE–ETI–RIS	100	30 days	43/–
Rabenda et al. (2008) [45]	Belgium	54,807	ALE	100	35 days	40/25
Sheehy et al. (2009) [67]	Canada	32,804	ALE–RIS	89–90	45 days	Previous fracture: Brand ALE/RIS: 61/ Generic ALE: 45/ No previous fracture: Brand ALE/RIS: 67/ Generic ALE: 39/–
Siris et al. (2006) [5]	USA	35,537	ALE–RIS	100	30 days	–/20
Solomon et al. (2005) [46]	USA	40,002	ALE–RIS–other	96	120 days	55/40
Ström et al. (2012) [47]	Sweden	17,647	ALE	84–88	56 days	Started treatment in 2006: 67/ Started treatment in 2009: 52/–
van Boven et al. (2013) [61]	Netherlands	8,610	ALE–ETI–IBA–RIS–other	76	30 days	59/46
van den Boogaard et al. (2006) [48]	Netherlands	14,760	ALE–ETI–RIS	100	7 days	44/27
Vanelli et al. (2009) [49]	USA	168,640	Not specified	91–94	30 days	Treatment-experienced: 45/ Treatment-naïve: 20/–
Wade et al. (2012) [63]	USA	33,558	ALE–IBA–RIS–other	94	90 days	45/–
Weiss et al. (2007) [56]	USA	165,955	ALE–RIS/IBA	100	30 days	ALE–RIS: 12/– IBA: 10/–
Weycker et al. (2006) [50]	USA	12,538	ALE–RIS–other	100	90 days	Weekly: 57/39 Daily: 50/33
Xu et al. (2013) [66]	USA	41,461	ALE–IBA–RIS–other	92–95	90 days	Commercial: 42/ MAPD: 41/–
Yeaw et al. (2009) [51]	USA	10,268	ALE–ETI–IBA–RIS–other	94	60 days	41/23
Yu et al. (2012) [52]	Taiwan	3,589	ALE–other	91	30 days	51/36
Ziller et al. (2012) [62]	Germany	195,191	ALE/ETI/IBA/RIS	86–92	183 days	ALE 70 mg: 45/ ETI: 43/ IBA 150 mg: 51/ RIS 35 mg: 35/–

–, estimates are for all reported treatments; /, estimates are for separate treatments

ALE alendronate; *DIN-LINK* Doctors' Independent Network Database; *ETI* etidronate; *GPRD* General Practice Research Database; *IBA* oral ibandronate; *MAPD* Medicare Advantage Prescription Drug; *MEDIPLUS* IMS Disease Analyzer, *not specified* no reporting for specific oral bisphosphonates, *other* other anti-osteoporosis treatments (e.g., strontium ranelate, raloxifene, zoledronate, and hormone replacement therapy), *RIS*, risedronate

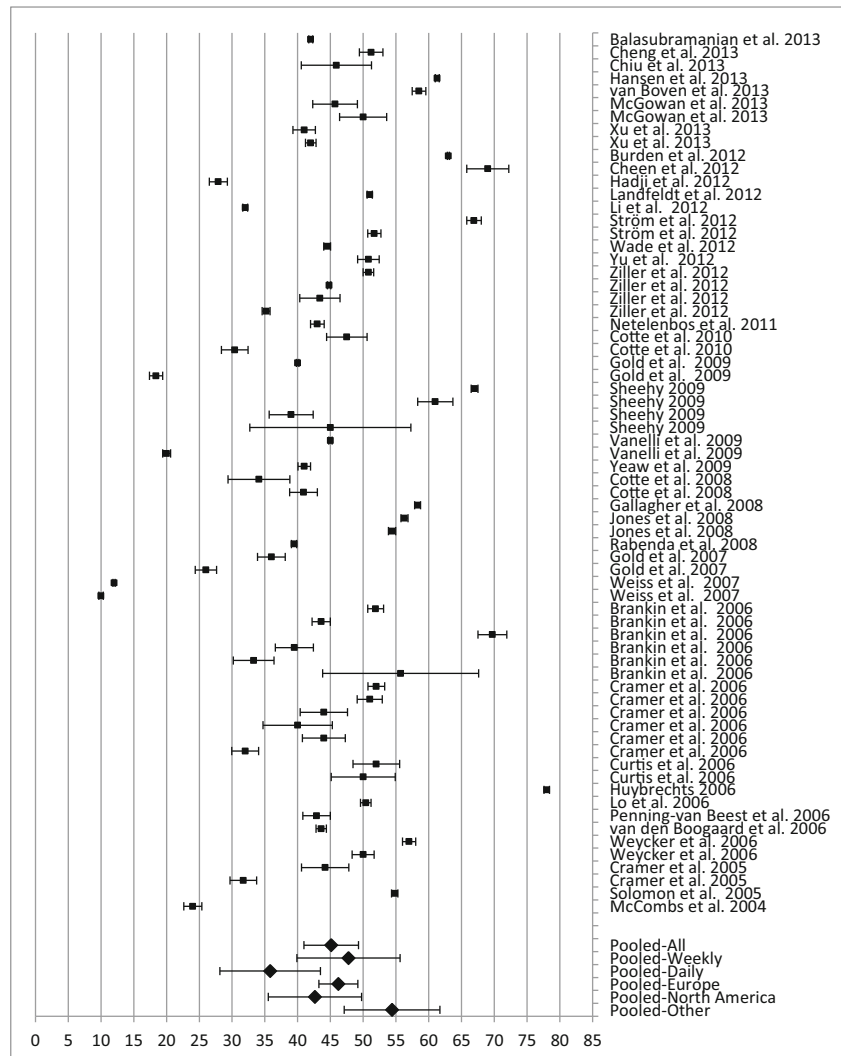
first retrospective register study of persistence among Swedish women in whom denosumab therapy was initiated for the treatment of PMO. Twelve-month persistence with denosumab treatment was 83 %. This result is similar to previously reported estimates of persistence with denosumab [15–17] and is higher than previously published estimates of persistence with oral BPs. Indeed, this study's pooled estimate

from 39 studies of oral BPs showed that only 45 % of patients were persistent with treatment after 12 months.

Persistence with denosumab

The women included in our database study were slightly older than those included in a study of treatment-naïve users of oral

Fig. 4 Estimates of 12-month persistence with oral bisphosphonate treatment *black square* individual study, *black diamond* pooled estimate. Data are given as percentage (95 % confidence interval). Citation numbers of the studies detailed in this figure are given in Table 3



BPs which also used the same database [6, 47]. Additionally, the majority of women in our study had previously received other anti-osteoporosis therapies; this is not surprising given that most women are prescribed oral BPs as their first line of treatment and subsequently switch to another treatment if they do not respond or experience intolerable side effects or dosing inconvenience. We estimated 12- and 24-month persistence with denosumab therapy to be 83 and 62 %, respectively, using a permissible gap of 56 days (8 weeks). The length of this gap is somewhat arbitrary and was chosen to be consistent with that used in previous studies of persistence using the same database [6, 47]. Varying the permissible gap to 30, 90, and 180 days resulted in estimated persistence rates of 78, 84, and 87 %, respectively, at 12 months, indicating that the estimates were robust.

Women who had received previous anti-osteoporosis therapies were more likely to persist with denosumab than treatment-naïve women. One possible explanation for this finding is that treatment-experienced women are more informed about

their disease and receive more information from their prescriber. Filling a prescription for calcium and/or vitamin D supplementation in the first 6 months after initiating denosumab was significantly associated with persistence, with those who filled prescriptions having a higher persistence rate than those who did not. Similar results were reported by Cotte et al. [33], who found that the rate of persistence was higher in women taking calcium and vitamin D supplementation than in those who did not take such supplements. While the reason for this is not clear, a possible explanation is that calcium and vitamin D supplementation is an indicator of high risk and, therefore, high disease awareness. Finally, women receiving glucocorticoids before initiating denosumab had lower rates of persistence than those who had no experience of glucocorticoids. Similar results have been reported elsewhere for other anti-osteoporosis treatments [6, 44, 53], and further study is warranted to elucidate the reasons for the association between persistence and glucocorticoid use.

Persistence with oral bisphosphonates

The literature review 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. Other study design heterogeneities concerned the possibility of a patient accumulating prescriptions or switching between dosages, dosing intervals, types of BP, and differences in study population. Less obvious differences, which were not systematically captured in our review, related to data quality and completeness, under-reporting by family physicians, and administrative hurdles. As well as methodological heterogeneity, the results are likely to have been influenced by other factors, such as types of healthcare organization, approaches to patient monitoring, drug reimbursement levels, and population disease awareness.

The pooled estimate from our literature review showed that 45 % of patients were persistent with oral BP therapy after 12 months. This relatively low persistence can possibly be explained by the asymptomatic nature of osteoporosis [68] and the complicated administration of oral BPs, whereby the tablet is taken under fasting conditions and with the patient remaining in an upright position for about an hour to avoid oesophageal reflux and oesophagitis, which, although infrequent, has been reported [69].

The two Swedish studies identified in the literature review were based on the Swedish Prescribed Drug Register. They estimated 12-month persistence with oral BPs to be 51 and 67 %, and 24-month persistence to be 25 % [6, 47]. It is worth noting that the estimate of 67 % was derived before the introduction of generic alendronate, which is likely to have caused a drop in persistence. These estimates for persistence with oral BP therapy are lower than the rates observed with denosumab using the same database. The permissible gap was identical to that in the present study (56 days); the only major difference was that patients were allowed to accumulate medicine in the studies of oral BPs.

Limitations

While retrospective register studies are based on historical prescription data and, hence, avoid the reporting bias that can arise in prospective studies, pharmaceuticals administered in hospitals are not captured by the Swedish Prescribed Drug Register and thus have not been included in our analysis. It is estimated that less than 10 % of sold denosumab doses have been administered in hospitals. By not including denosumab administered in hospitals, we may have not identified women who started treatment earlier than was recorded in the database and so we may have underestimated the true persistence rate;

however, these women may be atypical and, to a large extent, may have been given denosumab for reasons related to cancer diagnoses. A register of prescriptions does not provide any assurance that the dose was actually taken; therefore, persistence with denosumab may have been overestimated in this study. Another limitation of retrospective data is that all variables of interest may not be available, and it was not possible in this database analysis to control for bone mineral density, concomitant medicine use, comorbidities, lifestyle factors, and socioeconomic variables, all of which may be important predictors of persistence [57].

The literature review included all identified retrospective studies on oral BPs that reported at least one estimate of either 12- or 24-month persistence, with no other quality requirement for inclusion. Some persistence estimates may consequently have been derived from data of insufficient quality for a robust analysis. In addition, there was heterogeneity between the studies. With this in mind, the pooled estimates and the comparisons between the studies need to be interpreted with some caution. Moreover, the analysis did not consider persistence with other anti-osteoporosis drugs such as zoledronic acid and intravenous bisphosphonates. Persistence with these treatments, which are administered less frequently than oral BPs, has previously been shown to be higher than with oral BPs [62].

Conclusion

Persistence with denosumab in women with PMO in Sweden was found to be approximately two-fold higher than pooled persistence rates from a meta-analysis of retrospective data on oral BPs. Our results from clinical practice are consistent with previous reports of persistence with denosumab, in both a clinical trial setting and studies of routine practice.

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Conflicts of interest LK and OS have previously consulted for companies marketing products for osteoporosis. JL, EP, and MI are employed by Amgen Inc.

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