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ORIGINAL ARTICLE

Long-term persistence in patients with osteoporosis receiving denosumab in routine practice: 36-month non-interventional, observational study

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Abstract

Summary Persistence rates over 36 months with denosumab in patients diagnosed with osteoporosis in a real-world setting were examined, along with baseline patient characteristics predictive of persistence. This study represents the longest observational period with denosumab persistence and shows higher persistence rates when compared to bisphosphonates.

Introduction The study objective was to describe long-term persistence with denosumab among patients treated for osteoporosis in a real-world setting. We also sought to examine patient characteristics predictive of persistence. Lastly, this study attempted to place the results in context by conducting a literature review of published persistence data for denosumab.

Methods This retrospective, non-interventional study analyzed 1158 patients from a specialty community private practice to assess patient persistence with denosumab in routine care. Persistence was defined as receiving seven denosumab injections, using an 8-week permissible gap, over 36 months. Non-persistent patients were further investigated retrospectively to identify reasons for discontinuation, when available.

Results Demographic analysis showed a population of 1158 patients with mean age 68.4 years old and baseline T-score − 2.7; nearly half of which experienced a prior osteoporosis-related fracture. In a Kaplan-Meier survival analysis, 36-month persistence overall was 50.7%. Net persistence, as defined by receiving seven injections in the allowable time frame, was 64.2% of the cohort. In a multivariate analysis, prior vertebral fractures and recent osteoporosis therapy were associated with higher persistence; age greater than 75 years was associated with non-persistence. Reasons for discontinuation were available in 91.6% of non-persistent patients and categorized to include the ten most common explanations.

Conclusion This study to our knowledge represents the longest continuous observational period providing data on denosumab persistence in a real-world setting. The total persistence noted is quite robust when compared to bisphosphonates and is within the upper range of prior published studies of denosumab with shorter observation periods.

Keywords Denosumab · Osteoporosis · Persistence · Real-world data · Treatment

Introduction

The pathology of osteoporosis reflects a chronic, progressive process depicted by bone loss and structural deterioration conferring a fracture burden to an estimated 10 million Americans [1, 2]. Currently, bisphosphonates remain the most commonly prescribed medications for patients with osteoporosis. Unfortunately, adherence and compliance with oral bisphosphonate treatment is poor; discontinuation rates approaching 80% by 2 years [3–5]. Despite large-scale educational efforts, persistence with these agents remains unacceptably low, rendering our pharmacologic advances suboptimal in reducing the societal burden of fragility fractures [6, 7]. The issue of poor compliance not only directly impacts fracture rates and

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associated morbidity/mortality but also contributes to soaring health care expenditures [8–11]. New strategies to improve compliance are thus a worthy pursuit and parenteral longer-acting therapies have entered the marketplace in an attempt to meet this goal.

Among these newer agents is Denosumab (Prolia®, Amgen, Thousand Oaks, CA), a human monoclonal antibody against receptor activator of nuclear factor κ-B ligand (RANKL). By inhibiting cytokine-mediated osteoclastogenesis, denosumab potently attenuates bone dissolution [12–14]. A single subcutaneous injection of denosumab administered at 6-month intervals results in decreased bone resorption and greater bone mineral density (BMD) when compared to either placebo or bisphosphonates [15]. Moreover, denosumab treatment has been demonstrated in clinical trials to significantly reduce, over 3 years, the incidence of new vertebral, non-vertebral, and hip fractures as compared to placebo [14]; with safety data available in an open-label extension trial extended to 10 years [16].

Osteoporosis is a chronic protracted condition; thereby ensuring compliance over the long term remains a critical therapeutic goal. To date there have been relatively few studies addressing whether administering denosumab twice yearly in real-world clinical settings achieves this goal. Most of the studies reported to date describe patient's medication-taking behavior for 12 or 24 months, which in reality translates to one or, at most, three doses after initiation of therapy. There is an urgent need to determine whether patients, outside of clinical trials, will comply with a therapeutic regimen involving injections bi-annually over a more prolonged period of time.

The current study was undertaken to describe our experience at a consultative practice treating patients with denosumab as part of routine care for osteoporosis, assessed over approximately 3 years. To our knowledge, no study published to date provides persistence data in a sizeable cohort over a 3-year observation period. Understanding the scope of issues that impact adherence with newer pharmacotherapies and modes of administration over prolonged periods of time are critical to refine future strategies to promote skeletal health and reduce the burden of fractures in our society.

Methods

This non-interventional observational based study included patients being treated for routine care at a community office that specializes in osteoporosis as a major focus of rheumatologic care, and hence intended to reflect real-world data. The study cohort consisted of all women and men with an ICD-9/10 diagnosis of osteoporosis who initiated denosumab and received at least one injection at our facility for treatment. Every patient was then followed over at least a 36 months, with allowance for grace periods after each scheduled injection (see below). Persistence was then determined among patients given denosumab as prescribed over this time span. Treatment was assigned prior to and entirely independent of this observational study; outcomes are recorded during routine practice. All injections administered and recorded were subsequently extracted retrospectively from an electronic medical record database (EClinicalworks, Westborough, MA) between the years 2011 and 2018.

Study population

The index period used for the subject's first denosumab dose was between the dates of January 2011 and December 2014. The last follow-up date was November 27, 2018. The date of the first denosumab injection was defined as the cohort entry date. An 8-week permissible grace period was given for each injection date, with a sensitivity analysis performed for 4-, 6-, and 8-week grace periods. Inclusion criteria required a diagnosis of osteoporosis in postmenopausal females or males who were deemed to be at high risk for fracture as determined by a low T-score on bone density measurements, and/or using the fracture assessment risk (FRAX) tool (www.shef.ac.uk/frax/) or a history of prior fractures. In this cohort, patients receiving denosumab to prevent bone loss in the setting of hormone depletion therapy as adjunct treatment for breast or prostate cancer or during a course of glucocorticoid therapy were not included. All patients were seen for an office visit immediately prior to drug administration by an experienced clinician during which relevant laboratory results were reviewed and any patient concerns related to therapy or the underlying disease were addressed. Standard patient information was recorded by a clinician as part of routine clinical practice into the electronic medical records (EClinicalworks, Westborough, MA) at each visit, including demographics, family history, comorbidities, concomitant medications, previous osteoporosis treatments, prior or incidental fractures, BMD, and FRAX. Denosumab was administered by clinic personnel as a subcutaneous injection. Subjects were then scheduled a follow-up appointment for 6 months to receive their next dose along with an office visit during which time importance of adherence was emphasized. Bone densities were done at our facility every 12–24 months at the time of the visit when possible and reviewed during the office visit. Automated phone calls were used to confirm patient appointments 1 day before their next visit and shortly following any canceled or no-show visits.

Assessment of persistence and discontinuation rates

Adherence to denosumab therapy was assessed as an outcome synonymous with persistence and compliance. Outcomes included adherence over a 36-month period of follow-up for each individual patient. Incident denosumab users were

defined as "persistent" if they received seven injections over this time period. A permissible gap of up to 8 weeks between repeat injections was allowed as in prior studies [17–28]. To explore the effects of different permissible gaps on denosumab persistence, we used 4-, 6-, and 8-week gaps and a sensitivity analysis was performed. Persistence was defined as conforming to medication duration of time from initiation to discontinuation of therapy, censoring for death. We assessed the proportion of patients that received a second, third, fourth, and so forth injection during the allowable time frames, described above.

Predictors of adherence

Potential predictors of denosumab usage were determined at cohort entry among the entire population. The variables included age, gender, body mass index (BMI), age of menopause (when available), prior osteoporosis treatment in recent (prior 18 months) or remote past (more than 18 months elapsed), prior fractures (vertebral, non-vertebral, and hip), comorbidities (> 3 chronic conditions), concomitant medications (> 3 considered polypharmacy), and T-scores at time of initiation of therapy. Dual-energy X-ray absorptiometry (DXA) scans were performed on all patients in this cohort prior to initiation of therapy (Hologic Discovery 4500A, Marlborough, MA, when done at our facility). The lowest T-score at either the lumbar spine, total hip, or femoral neck was considered the major determinant for treatment and thus recorded for the analyses. In addition, patients considered as being at ultra-high risk of fracture, defined arbitrarily as having either a FRAX-derived calculated risk of hip fracture that exceeded 6% or a T-score ≤ − 3.5, was explored as an additional variable for persistence. Lastly, we determined whether a significant incremental increase in an individual's bone density measurement on first follow-up DXA (within 24 months of initiating therapy, when available) impacted persistence. We considered an increase of > 5% at either the L1–4, total hip, or femoral neck region of interest (ROI) as a binary variable equating with a clinically significant increase (at our facility, this substantially surpassed least significant change at 95% confidence interval at each ROI). Along the same lines, we recorded if a decrease of > 5% at any ROI impacted on persistence. The bone density results were discussed with each patient in detail during the office visit. Lastly, reasons for discontinuation of denosumab were obtained when available from reviewing each individual chart or by contacting and interviewing patients by phone.

Statistical analysis

Demographic and clinical characteristics of denosumab users were summarized. Both descriptive and predictive analyses were performed. Demographic data were summarized by providing mean and standard deviation for continuous variables, and frequency and proportion for categorical variables. Metrics for persistence rates were explored and compared through all steps of analysis; testing both Kaplan-Meier estimator and aggregate net persistence of one through seven injections over the study period as some patients resumed regular scheduled therapy after a period of absence.

Sensitivity analyses were conducted for differing permissible gaps to determine the effects on persistence rates. The sensitivity analyses were performed under both persistence metrics to characterize their differences. All pairwise correlations of covariates were calculated. Chi-square statistics were calculated comparing populations of single categorical attributes with persistence. Subsequently, univariate effects on both metrics of persistence were quantified using logistic regression.

Multivariate logistic regression analysis was used to assess predictability of persistence from the baseline characteristics and quantify collective importance of collected covariates. Additionally, accuracy of logistic regression predictors for both persistence metrics was compared.

Results

Demographic and patient clinical characteristics

The baseline characteristics of the patients are as follows (for full details, see Table 1). Most patients (96.3%) were female. The mean (SD) age of the population at initiation of therapy was 68.4 (± 10.4) years and were predominantly Caucasian (95.4%). Mean baseline T-score at initiation of therapy was − 2.7 (± 0.61); 10.6% of patients had prior vertebral fractures, 5.6% of patients had prior hip fractures, and 33.28% had non-vertebral fractures. Nearly half (49.3%) of patients had received prior osteoporosis therapy within 18 months of initiation of denosumab therapy while 29.5% received prior therapy but not in the previous 18 months. Less than half (41.4%) of the cohort was considered to be at a remarkably high risk of future fracture, as arbitrarily defined by either a baseline FRAX of > 6% at the hip or a baseline T-score ≤ − 3.5.

Persistence at 36 months with denosumab

The percentage of patients that persisted with denosumab over 36 months (equal to receiving subsequent injections within 6 months ± allowed permissible gap) are represented using Kaplan-Meier estimates of persistence with permissible gaps of 4, 6, and 8 weeks (Fig. 1). Using a permissible gap of 8 weeks, patient persistence with denosumab therapy was 76.9% at 12 months, 67.3% at 18 months, 59.6% at 24 months, 54.1% at 30 months, and 50.7% at 36 months. Using permissible gaps of 4 and 6 weeks, persistence at months 12 and 36

Table 1 Baseline Characteristic of Patients (n = 1,158)

Clinical Parameter	All Patients, n(%) or Mean (±)
Demographics	
Gender	
Female	1,115 (96.29)
Male	43 (3.71)
Age (yr)	68.35 (10.44)
Age >65 (yr)	683 (58.98)
Age >75 (yr)	322 (27.81)
Ethnicity/Race, n (%)	
White or Caucasian	1,105 (95.42)
Hispanic or Latino	33 (2.85)
Black or African-American	13 (1.12)
Asian	5 (0.43)
Age at Menopause (yr)	48.13 (5.81)
BMI (kg/m^2)	25.72 (5.45)
Previous osteoporosis treatment	
Within last 18 months, prior to index period	570 (49.27)
Past theraphy (>18 months prior to index period)	341 (29.47)
None	247 (21.33)
Prior Fractures, n (%)	
Vertebral fracture	123 (10.63)
Hip fracture	65 (5.62)
Nonvertebral fracture	385 (33.28)
Comorbidities, n (%)	
≥ 3 chronic diseases	354 (30.6)
Concurrent polypharmacy, n (%)	
≥ 3 chronic medications	438 (30.6)
BMD test result[a], n (%)	
t-score at baseline	−2.66 (0.61)
Parameters suggestive of excessive fracture risk, n (%)	
FRAX at hip ≥ 6%	478 (41.42)
t-score ≤ −3.5	94 (8.14)
Clinical response to treatment[b], n (%)	
BMD gain ≥ 5% following baseline DXA	656 (63.94)
BMD loss ≥ 5% following baseline DXA	67 (6.53)

[a] data represent lowest t-score from regions of interest (ROI) including L1−L4, total hip, or femoral neck which directed therapy

[b] data represents change in BMD from baseline DXA (obtained immediately prior to initiation of therapy) to first follow-up DXA exam (performed at 12−24 months interval); gain or loss at any ROI

were 70.1–39.8% and 74.6–47.5%, respectively. A total of 555 (49.3%) patients were non-persistent with denosumab at 36 months ± 8 weeks.

Net persistence with denosumab (equal to the total amount of injections that fulfilled an interval of 6 months ± allowed permissible gap) was 64.2% for seven injections every 6 months ± 8 weeks. Using a permissible gap of 8 weeks, net persistence was 85.6% for three injections, 78.4% for four injections, 72.4% for five injections, and 68.1% for six injections. Using permissible gaps of 4 and 6 weeks, 56.1% and 62.1% of patients received seven injections, respectively. A total of 403 (35.8%) patients did not receive a total of seven injections within a 6 month ± 8 week interval. For comparative purposes, a literature review (using PubMed database) was performed for publications related to denosumab persistence under varying observation periods as summarized in Table 3.

Frequency of denosumab injections

The median (Q1, Q3) number of denosumab injections received by patients was 7 (4, 7) overall. The mean (SD) number of denosumab injections was 5.6 (± 2). Most patients (62.5%) received seven injections over the 36-month (± 8 weeks) interval. A total of 434 (37.5%) of patients did not receive a total of seven injections of denosumab within an allowable 36 month ± 8 week permissible period.

Multivariable analysis of factors associated with 36-month adherence

The results of the analysis for the baseline covariates are presented in Fig. 2, which plots the odds ratio and 95% confidence intervals (CI) for each baseline variable (independent variable). Odds ratios > 1 indicate a characteristic associated with higher persistence, and odds ratios < 1 indicate a characteristic associated with lower persistence. The only significant baseline covariate associated with non-persistence at 36 months was age greater than 75 years (odds ratio = 0.68, p = 0.003). Significant covariates associated with higher persistence at 36 months were recent osteoporosis therapy (odds ratio = 1.43, p = 0.005) and prior vertebral fracture (odds ratio = 1.54, p = 0.05).

Discontinuation

Exploratory analyses following extensive chart review and patient interviews revealed the major reasons for discontinuing denosumab therapy, as enumerated in Table 2. Of the 432 patients non-persistent with denosumab, reasons for discontinuation were obtained from 396 patients (91.6%). Of these 396 patients, approximately one third (33.1%) were censored due to death, continuing injections elsewhere or relocated without further information available. Nearly half the patients (49.7%) discontinued based on individual decisions or belief systems, including deprioritizing the need for therapy, forgetfulness, neglect, fear of anticipated side effects, or perceiving a side effect. Another group of patients stated that drug-related costs were prohibitive. In about a fifth of the patients (19.7%), discontinuation was attributed to the development of concomitant illnesses or was advised by another healthcare provider to halt or change therapies, including issues related to coordinating dental procedures.

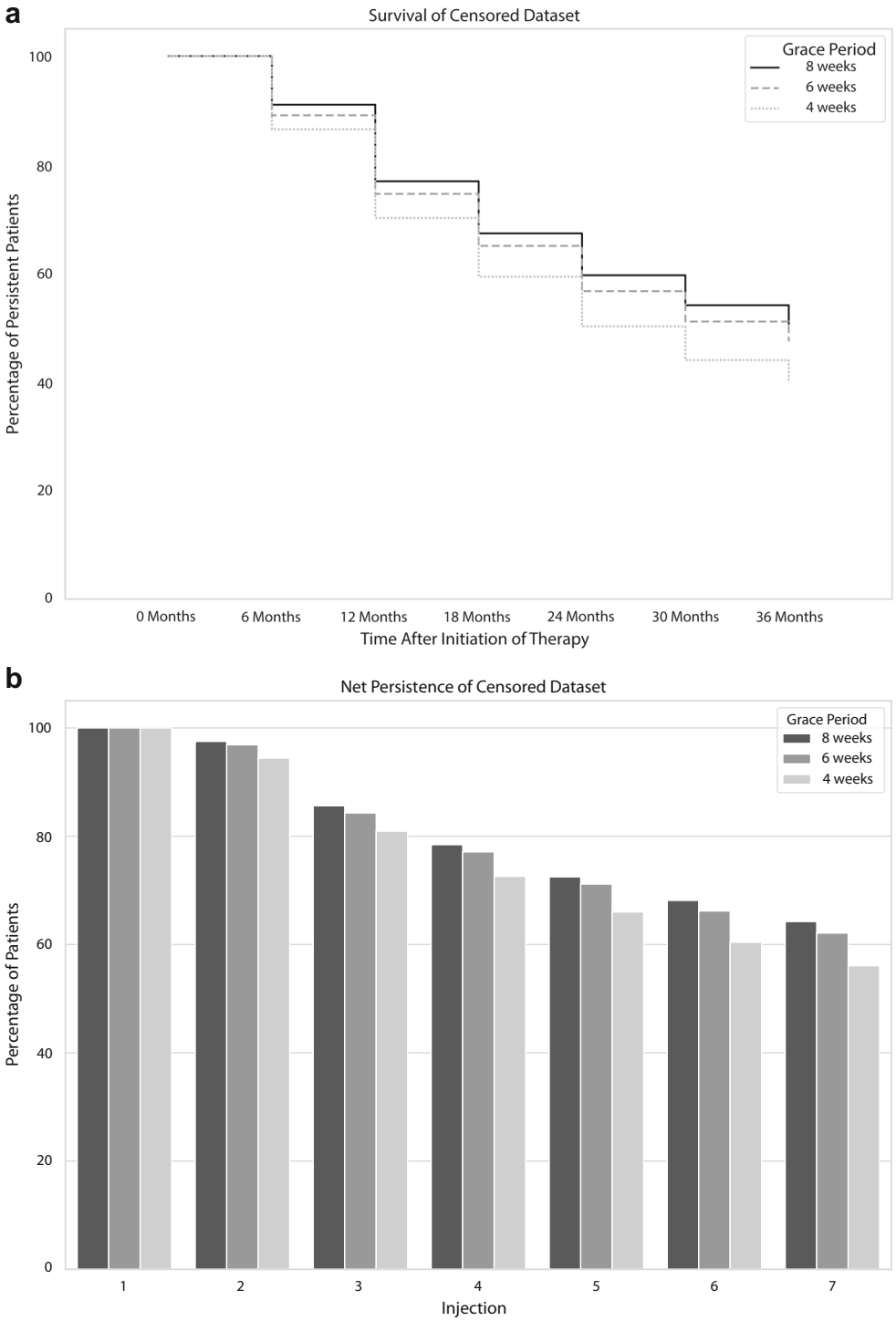

Fig. 1 **a** Kaplan-Meier estimates of persistence with denosumab with 4-, 6-, and 8-week permissible gaps. **b.** Net persistence with denosumab over 36 months with 4-, 6-, and 8-week permissible gaps. Net persistence was defined as the total amount of injections (i.e., one to seven injections) that fulfilled an interval of 6 months ± allowed permissible gap (i.e., 4, 6, and 8 weeks)

Discussion

The importance of drug adherence in treating osteoporosis to achieve the goal of fracture prevention is well-recognized and emphasized in numerous prior publications [6, 7, 9, 10, 29]. Research to date has provided extensive data indicating that persistence and compliance with osteoporosis pharmacotherapy is suboptimal, despite the abundant evidence that persistence results in fewer fractures [5, 30]. Factors determining persistence are not fully understood but are likely to be multifactorial, including, but not limited to, medication costs, dosing requirements, side effects, perceived harm from drug treatment versus disease, patient-physician relationships, and patients' inability to notice improvement in an asymptomatic disease [31].

Several published studies have demonstrated low persistence rates among patients treated with bisphosphonates as

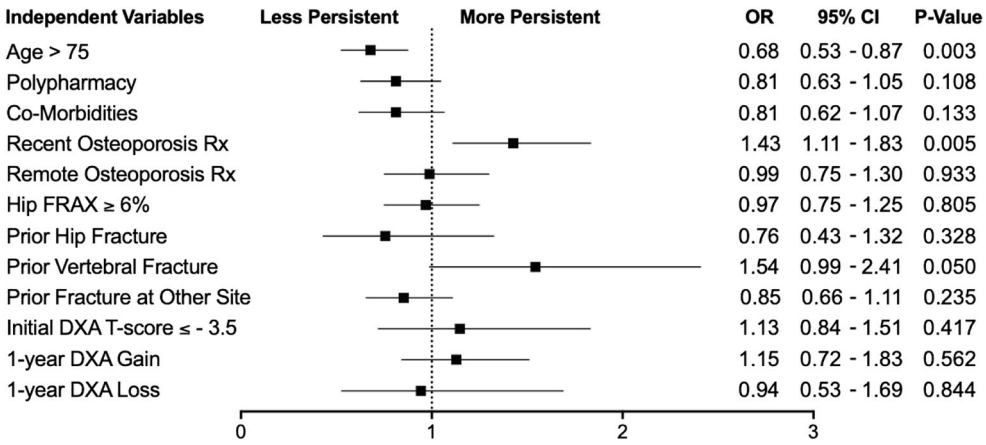

Fig. 2 Logistic regression analysis of 36-month persistence with denosumab

compared to denosumab [7, 32]. Most of the prior observational studies, notwithstanding, are limited to time periods of 24 months or less. Longer-term observational periods are rarely described (Table 3). Adherence with denosumab over the long haul requires further scrutiny for several unique reasons. First, the safety and efficacy data that emerged from the 10-year extension of the pivotal registration trial provides clinicians reassurance in continuing the drug over time [33]. Moreover, the recent recognition that discontinuation invariably results in rapid decline in bone density and in some individuals leads to multiple vertebral fractures [14, 34]. Indeed, current therapeutic strategies endorse continuous treatment with denosumab (over prolonged periods) and discourage a drug holiday [34–37]. Thus, longer-term adherence data in real-world settings are invaluable in estimating the potential for denosumab to have a significant impact on this widespread public health issue.

Table 2 Reasons for discontinuation ($n = 396$)

Reason	Number of patients, *n* (%)
Censorship	131 (33.1)
Deceased	77 (19.4)
Continues injections elsewhere	38 (9.6)
Relocated without available information	16 (4.0)
Individual patient decision	197 (49.7)
Need for therapy deprioritized/forgetfullness[a]	74 (18.7)
Financial issues (drug-related costs)	54 (13.6)
Perceived side effect	52 (13.1)
Fear of anticipated side effects	17 (4.3)
Clinical issues	78 (19.7)
Concomitant disease	27 (6.8)
Advised by provider to discontinue	26 (6.6)
Planned dental procedure prompted rescheduling	15 (3.8)

[a] These reasons, which included forgotten appointments, neglect, perceiving osteoporosis as low priority, personal preferences, and no change noted in symptoms, were often reported together, and thus are considered as a single category

This retrospective, non-interventional observational study provides real-world data from routine clinical practice of long-term denosumab adherence over a 36-month time period. In this group of osteoporotic individuals, extended treatment with denosumab yielded considerably higher rates of persistence than what has been observed with earlier therapeutic options such as oral bisphosphonates [17, 22, 24, 28].

In this study, patient persistence after 36 months was 64.2% ($n = 743$) overall, as defined by seven total injections received using an 8-week grace period. A sensitivity analysis, adjusting the permissible gap to 4 and 6 weeks, revealed the anticipated decline in persistence, although the magnitude was relatively small (56.1% and 62.1%, respectively). Given the difficulties and divergent methods in defining persistence for a medication given every 6 months, we calculated persistence either as a net value or as a stepwise "survival" function. In the former, all injections received in the study period were counted regardless of when they occurred, whereas in the latter, doses given after a permissible gap were disregarded. The different persistent rates determined from these methodologies (50.7% versus 64.2%) should be noted, as a considerable number of patients failed to receive doses timely but then subsequently were adherent with therapy. With either methodology, there appeared to be a steady decline in persistence over 3 years with the largest discontinuation noted over the first 12 months of therapy.

Predictors for lack of persistence with denosumab included polypharmacy (taking more than three medications concomitantly) and age greater than 75 years. It is well recognized that when patients are required to take multiple drugs, compliance and adherence often decline dramatically. This is likely due to the burden of taking multiple medications for chronic conditions and not perceiving osteoporosis treatment as a priority, as noted by others [21]. The fact that an excess of comorbidities trended toward poor persistence, although it did not reach significance, is consistent with this concept. Moreover, we

Table 3 Prior studies of denosumab persistence

Publication	Length of observation period	Permissible gap[a]	Study design	Source of subjects	Region	Subjects (*n*)	Mean age (SD)	% fragility fractures at baseline	Persistence (%)
Cheng et al. (2015)	12 months	8 weeks	Retrospective	Commercial/Medic-are claims database	USA	1235	70.1 (11.8)	16.8 (fragility fx)	68.3
Durden et al. (2017)	24 months	60 days (~8 weeks)	Retrospective	Commercial/Medic-are claims database	USA	3599	68.4 (11.1)	10.9 (fragility fx)	41.2
Fahrleitner-Pammer et al. (2017)	24 months	8 weeks	Prospective	Multicenter clinical practices	Germany/Greece/ Belgium/Austria	1479	66.3 (9.2)–72.5 (8.7)	19.9 (vertebral), 4.6 (hip), 37 (non-vertebral)	75.1–86
Karlsson et al. (2015)	24 months	56 days (~8 weeks)	Retrospective	National claims database	Sweden	2315	73.7 (9)	N/A	62
Lakatos P et al (2016)	24 months	8 weeks	Retrospective	National claims database	Hungary	1104	N/A	N/A	38.4
Modi et al (2017)	24 months	60 days (~8 weeks)	Retrospective	Commercial claims database	USA	617	73.5 (7.8)	10.4 (fragility fx)	28.3
Papaioannou et al. (2015)	24 months	8 weeks	Prospective[b]	Multicenter, voluntary patient support program	Canada	1676	73.7 (10.6)	42.5 (fragility fx)	59.1
Petranova et al. (2017)	24 months	60 days (~8 weeks)	Retrospective	Multicenter clinical practices	Bulgaria	224	63.4 (7.74)	72.4 (vertebral), 6.9 (hip), 15.8 (non-vertebral)	98.7
Silverman et al. (2018)	24 months	8 weeks	Prospective	Multicenter clinical practices	USA /Canada	935	70.8 (9.9)	16 (vertebral), 42 (non-vertebral)	58
Tremblay et al. (2016)[a]	24 months	56 days (~8 weeks)	Retrospective	National claims database	Canada	6032	74.9 (9.3)–75.5 (9.9)[c]	4.7 (vertebral), 9.4 (hip), 9.7 (non-vertebral)[d]	63.3
Fuksa et al. (2015)	30 months	60 days (~8 weeks)	Retrospective	National claims database	Czech Republic	6081	N/A	N/A	34
Migliaccio et al. (2017)	N/A	8 weeks	Prospective	Multicenter clinical practices	Italy	870	70 (9.5)	72.4 (vertebral), 6.9 (hip)	91.4
Current study	36 months	8 weeks	Retrospective	Single-center clinical practice	USA	1158	68.35 (10.44)	10.63 (vertebral), 5.62 (hip), 33.28 (non-vertebral)	64.8

N/A not available or provided

[a] Permissible gap of 8 weeks shown for comparative purposes across studies; note that most studies performed sensitivity analyses using differing permissible gaps

[b] Interventional study; the remainder of the studies are non-interventional by design

[c] Mean age provided for males and females

[d] Calculated over 5 years prior to therapy

noted that age greater than 75 years was associated with lower persistence. The literature has varied on the relationship between age and persistence, but others have noted similar findings [21, 31, 38]. It is certainly arguable that as older patients lose independence and mobility, they become more challenged in traveling to a facility to receive medication every 6 months. Of note, in our local region, patients often need to commute considerable distances. Additionally, many elderly patients spend their winters at southern locations in our country (colloquially termed "snowbirds"), which further complicates scheduling timely appointments. We noted that prior fractures or having an "ultra-high" risk for fracture (by FRAX calculation or T-score ≤ -3.5) did not appear to influence persistence [28], albeit a history of prior vertebral fractures reached significance as a predictor of higher persistence. A history of recent use of osteoporosis medications at baseline was predictive of persistence, consistent with the findings of others [21, 22, 25, 27, 28]. Some have suggested that a possible explanation for this finding is that treatment-experienced patients may indeed be more informed about their disease [22].

Lastly, we sought to ascertain whether a substantial gain in bone density (or loss), as discussed with the patient, would influence persistence. We anticipated that providing a patient with feedback of a BMD gain would likely provide incentive for adherence. This did not appear to be the case in our cohort. Although others have reported that obtaining bone density itself promotes persistence [39], the literature is scant on the impact of monitoring over time [40]. It is also somewhat disconcerting that patients arbitrarily characterized as ultra-high risk were no less likely to discontinue their therapy, albeit the numbers in these subgroups are smaller and the results should be interpreted with caution. It is conceivable that more patient education and support to promote better understanding of risk and therapeutic efficacy may be warranted.

Reasons for discontinuation were retrievable from the vast majority of the non-persistent patients and, after censoring for death, a variety of explanations were provided including perceived drug side effects, financial concerns, concomitant medical problems, dental issues, fear of side effects, and personal priorities or simple neglect. It is well recognized that, from the osteoporosis patient's perspective, a major barrier to prescription treatment includes a fear of possible side effects [41]. Financial limitations were also prevalent, and it is certainly plausible that more patients were influenced by financial constraints but chose not to disclose their concerns. Payment issues should be kept in mind when comparing persistent rates to countries with national health care systems and less individual patient financial demands. Another minor group of individuals reported being directed by other healthcare providers that treatment was unnecessary. Additionally, a small group of patients stated they continued receiving denosumab after relocation, but since this was not verified they were excluded from the persistent group data analysis.

Studies have shown a general patient preference toward denosumab when compared to treatments such as alendronate. The prospective, randomized denosumab adherence preference satisfaction (DAPS) study assessed 250 postmenopausal osteoporosis patients administered open-label denosumab or weekly alendronate for 24 months using a 12-month crossover comparative design and found that 90% of subjects preferred injectable denosumab and adherence with denosumab was statistically superior [33]. Our data, presented in the current analysis, is consistent with prior studies [17–28] although the range of persistence with denosumab reported to date varies widely (Table 3). The majority of the published studies have observed patients over 24-month periods of time with persistence rates varying from 28.3 to 98.7% (Table 3). This wide range may reflect disparate patient populations diverse in age, culture, and varying baseline fracture risks, differing drug costs and healthcare coverage systems, as well as size, design, and type of study. It also worthy of mention that "persistence rates" are defined with different methodologies in prior publications; thus, comparisons must be interpreted with a degree of caution. A recent publication reported remarkably high persistence rates in Bulgaria over 24 months, but the cohort was relatively small (224 subjects) and consisted of a very high proportion of patients with baseline fragility fractures which may influence the propensity to continue medication [26]. Migliaccio and colleagues also describe striking persistence rates in a similarly high-risk population with the vast majority having fragility fractures, but the recruitment index period extends to 2016—thus, the actual time period for observation remains unclear, as well as the number of subjects represented in the persistence rates over time as described [20]. In summary, longer-term studies are mostly non-existent to date, yet clearly warranted if we are to assess clinically meaningful persistence with this chronic disease. To our knowledge, the current investigation is the first to extend the full observation period to 36 months. No doubt, even longer periods of surveillance would be instructive in the future.

Strengths of this study, beyond its 36-month duration, is that it represents real-world data from more than a thousand patients receiving osteoporosis treatment as part of routine clinical practice, rather than an analysis of subjects who volunteered for a clinical trial or consented to participate in a prospective study which may inherently introduce a cohort selection bias [42]. In addition, relative to many studies of persistence with osteoporosis therapies taken at home by patients, the in-office administration allows for more accurate verification of medication delivery and thus compliance data. We also attempted to explore whether patients within our cohort, characterized as having a very high risk of fracture, demonstrated better adherence. Lastly, we probed the influence of bone density changes on medication-taking behavior in a subanalysis.

One of the limitations of this study is that the data represented is that of a single private practice in a suburban area and may not be generalizable to a broad spectrum of patients across our society. Other studies included patients treated with denosumab at locations in different countries and geographical regions, likely constituting a greater heterogeneity of patient demographics. Another limitation with retrospective data is that all covariates of interest may not be available for analysis such as socioeconomic class, educational level, lifestyle factors, and others, which may have influenced persistence. Furthermore, although our analysis attempted to determine if bone density changes with therapy influenced persistence, the study was neither designed nor powered to robustly address this specific question. Lastly, this study was also not designed to assess the association between persistence and risk of incident fractures, or to assess safety, or overall changes in bone density as a measure of efficacy in the cohort described.

In conclusion, this study shows that persistence with denosumab therapy over 36 months has a relatively low discontinuation rate as compared to most other pharmacotherapies utilized for osteoporosis in a routine clinical setting. This has the real potential to lessen the fracture burden and lower the morbidity and associated economic costs in our society [8, 43]. Nonetheless, further investigation and efforts are warranted to more fully optimize persistence with this long-acting treatment.

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Compliance with ethical standards

Conflicts of interest Daniel M Borek, Ryan C. Smith, and Conor N. Gruber declare that they have no conflict of interest. Barry L. Gruber has received honoraria from serving on the speaker bureau and advisory panels for Amgen, Inc., and Radius Pharmaceuticals.

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