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Original article

Persistence with denosumab therapy among osteoporotic women in the Canadian patient-support program

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Abstract

Objective:
The objective of this study was to evaluate persistence with denosumab among postmenopausal women with osteoporosis participating in the Canadian patient-support program (ProVital*). Denosumab is an injectable therapeutic option for osteoporosis that is administered subcutaneously every 6 months.

Methods:
ProVital, a support program in which patients voluntarily enroll, provides next injection reminder calls and educational material. A retrospective database analysis of patient self-reported data was conducted among osteoporotic women aged ≥50 who enrolled in the ProVital program and received their first denosumab injection between August 2010 and June 2011. To achieve 12 month persistence patients had to receive at least two denosumab injections, and to achieve 24 month persistence patients had to receive at least four denosumab injections, with consecutive injections no more than 6 months + 8 weeks apart. Logistic regression analysis was used to identify predictors of persistence.

Results:
A total of 1676 patients (mean age 74 years) were included. The 12 month persistence with denosumab was 81.6% (1367/1676 patients), and the 24 month persistence was 59.1% (991/1676 patients). Characteristics associated with both 12 and 24 month persistence were possession of private medication insurance and residence in Quebec. Additionally, age greater than 75, previous postmenopausal osteoporosis medication use, and fracture were associated with 24 month persistence.

Limitations:
Patient enrollment in the program was voluntary, so there may be selection bias for the patient population included in this study. Also, this study did not have a control group of patients who were not enrolled in a patient support program.

Conclusions:
The persistence with denosumab among patients enrolled in the program was higher than historical persistence with oral bisphosphonates, and similar to persistence of patients in an education program taking teriparatide, patients taking bisphosphonates in a pharmaceutical care program, and two observational studies of denosumab.

Introduction

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture[1]. Osteoporosis prevalence

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increases with age, and is estimated to affect approximately one in four Canadian women and one in eight Canadian men over age 50[2,3]. Osteoporotic fractures are associated with increased mortality and morbidity, are a cause of pain, and can have a negative impact on patients' daily functioning and quality of life[4–8]. Patients who have already experienced a fracture are also at increased risk for future fractures[9,10].

When treating osteoporosis, there is an emphasis on prevention of fragility fractures[11]. Canadian osteoporosis treatment guidelines recommend several pharmacotherapies for use in postmenopausal women, including bisphosphonates (alendronate, zoledronic acid, or risedronate), RANKL inhibitor denosumab, recombinant human parathyroid hormone 1-34 (teriparatide), the selective estrogen receptor modulator raloxifene, and hormone therapy[11]. Many Canadian osteoporosis patients with previous fractures do not receive appropriate therapeutic interventions[12], and adherence and persistence among patients prescribed osteoporosis medication are typically about 50% or less for treatment lasting a year or longer[13,14]. Further, the drug reimbursement environment in Canada is complex, and access to drugs can vary, depending on which province a patient resides in and what type of insurance coverage a patient has (e.g. private insurance, no insurance, or government insurance for specific medications)[15].

Patients who are not adherent (conform with day-to-day treatment recommendations) or persistent (continue treatment for prescribed length of time) with osteoporosis medication are at an increased risk of fracture, compared with adherent or persistent patients[16–19]. In addition, non-adherence results in greater use of health care resources and higher medical costs[20]. A variety of factors may influence patient adherence with osteoporosis medications, including adverse effects, medication costs, efficacy, injection route, injection frequency as well as doubts regarding the importance of their osteoporosis[21,22]. Strategies to increase communication between health care providers and patients could lead to improved adherence and persistence in the clinical setting[23–27].

Denosumab, a fully human monoclonal antibody, is an antiresorptive therapy for osteoporosis that functions by binding to RANKL, thus preventing osteoclast formation, function, and survival, thereby decreasing bone resorption[28]. In postmenopausal women with osteoporosis, denosumab reduces the incidence of vertebral, nonvertebral, and hip fractures[29], and improves bone mineral density at all measured sites. Denosumab was approved by Health Canada for the treatment of postmenopausal osteoporosis (PMO) in 2010. To date, limited information is available regarding persistence with denosumab outside of a clinical trial setting; therefore we examined persistence with denosumab among Canadian patients enrolled in the ProVital* program. This voluntary patient support program provides telephone reminders to patients prior to scheduled denosumab injections, along with patient counseling from trained nurses. It is possible that a disease management program that provides reminders and counseling to patients combined with a medication dosed every 6 months could lead to improved persistence.

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Patients and methods

Description of program

ProVital is a support program initiated in August 2010 in which patients voluntarily enroll. The program was developed and is funded by Amgen, and enrollment in the program is free for patients. It provides a nurse call-based reminder service to remind osteoporosis patients who were prescribed denosumab to book their next appointment at the prescribed 6 month interval. It also provides injection follow-up calls, counseling, and educational materials on the importance of pharmacologic and non-pharmacologic osteoporosis management. The program database served as the source of data for this study. Patients throughout Canada are eligible to enroll, and there are multiple routes of enrolment. Patients can enroll themselves by calling the program directly or by enrolling online. Contact information is included with the denosumab injection packaging. Physicians may enroll patients who agree to participate by directly contacting the program. Pharmacies that are participating in the program can enroll patients by checking a box in their system at the time that a patient fills a prescription. Approximately one in four Canadian patients prescribed denosumab were enrolled in the program as of December 2013[30].

Patients enrolled in the program may choose to be contacted by phone or email. Patients who choose to be contacted by phone receive a baseline call during which they are asked about their personal characteristics, fracture history and past osteoporosis medication use. Patients then receive reminder and follow-up calls for their denosumab injections, which are received every 6 months[31]. Data are collected from the patients during each telephone contact. Patients receive a reminder call 1 month prior to their next scheduled injection, and another call within 1 month following their scheduled injection to further capture relevant information, including if and when they received their injection. Additional telephone calls are scheduled if patients' injection appointments were rescheduled. Interviews are conducted by nurses, and data are entered into the electronic database by the interviewer as they are speaking with the patients. Additionally, patients are able to contact the program with product, disease, or adverse event related questions.

Selection of study participants

To be included in the study, patients were required to be female, 50 years of age or older, and have at least one injection with denosumab between 1 August 2010 to 30 June 2011. Women were not asked about their menopausal status; however, the study population was limited to women 50 years or above who were assumed to be post-menopausal. Patients were excluded if they were enrolled into the program more than 4 months following their first injection of denosumab to limit any recall bias between receiving the injection and answering questions about the injections. As limited information was collected from patients who received email reminders only (persistence was not collected), these patients were excluded from the study. Analysis was conducted after 16 June 2013 once patients were followed for a minimum of 717 days (18 months + 24 weeks) following their baseline injection, until they discontinued denosumab, were lost to follow-up, or died. The minimum of 18 months + 24 weeks was required so patients had three '6 month + 8 week periods' during which to measure the criteria for 24 month persistence (at least four denosumab injections, with consecutive injections no more than 6 months plus 8 weeks apart) described further below. During the analysis, patients were classified as lost to follow up if they had all of the following: 1) a program discharge description of 'patient unreachable' (attempts were made to contact a patient once a week, up to four times), 'patient does not want to participate in the program', or 'patient is a resident of long-term facility'; 2) no data for a subsequent injection or a program discharge date earlier than the scheduled date of the next injection; 3) no data showing that the patient was persistent with medication or of having discontinued or delayed treatment.

Study ethics approval

The study protocol received ethics approval and waiver of patient consent from the Institutional Review Board Services.

Persistence and discontinuation

To meet the study criteria for 12 month persistence, patients were required to have received at least two denosumab injections and to have taken the injections no more than 6 months plus 8 weeks (239 days) apart. Because a denosumab injection remains effective for 6 months, this measure was called 12 month persistence. To meet the criteria for 24 month persistence, patients were required to have received at least four denosumab injections, with consecutive injections no more than 6 months plus 8 weeks (239 days) apart. (As an example, a patient who received a first injection at time = 0 months, a second injection at time = 6 months, a third injection at time = 12 months, and a fourth injection at time = 18 months would meet the criteria for 24 month persistence, as an injection remains effective for 6 months.) These definitions were adopted from the Denosumab Adherence Preference Satisfaction (DAPS) randomized crossover study[32,33]. Individuals who were lost to follow-up were considered to be non-persistent, and they were included in the persistence calculations. However, an additional sensitivity analysis was conducted excluding the patients who were lost to follow-up from the persistence calculations. The reason for discontinuing treatment with denosumab was collected from the patient by the nurse during the telephone interview and was obtained from a pre-defined list of reasons (adverse event, patient decided not to continue with therapy, physician mandated, change in financial status, deceased, financial, switched therapy, lack of efficacy, change in insurance coverage, and treatment completed). When 'adverse event' was cited as a reason the information was forwarded to Amgen for entry into the Global Safety database. Due to patient confidentiality reasons, adverse event data specific to the patients in this program could not be analyzed for this publication. Amgen internal policies governing safety collection and surveillance require that adverse event information reported for patients in the program is captured in the Amgen Global Safety database. Amgen Global Safety conducts risk management reviews of denosumab throughout the product's lifecycle. These processes focus on the assessment, management, and communication of safety risks associated with denosumab that are identified through the signal detection and assessment process. This ensures continuous evaluation and management of the benefit–risk balance for denosumab, as well as timely communication of such safety information to health care providers, investigators, ethics committees, regulatory authorities, and patients that receive denosumab. Individual case reports were submitted to Health Canada's regulatory agency per reporting requirements.

All analyses were carried out using SAS 9.2 (Cary, NC, USA). Logistic regression analysis was performed to examine the relationship between patient characteristics (age, insurance type, previous fracture, risk factor score, province of residence, previous PMO medications, method of enrollment, and enrollment MD feedback) and persistence. Odds ratios for each explanatory variable along with their corresponding 95% (Wald-based) confidence intervals and p values were calculated. Odds ratios greater than 1 indicated that a variable was associated with higher persistence, and odds ratios less than 1 indicated that the variable was associated with lower persistence.

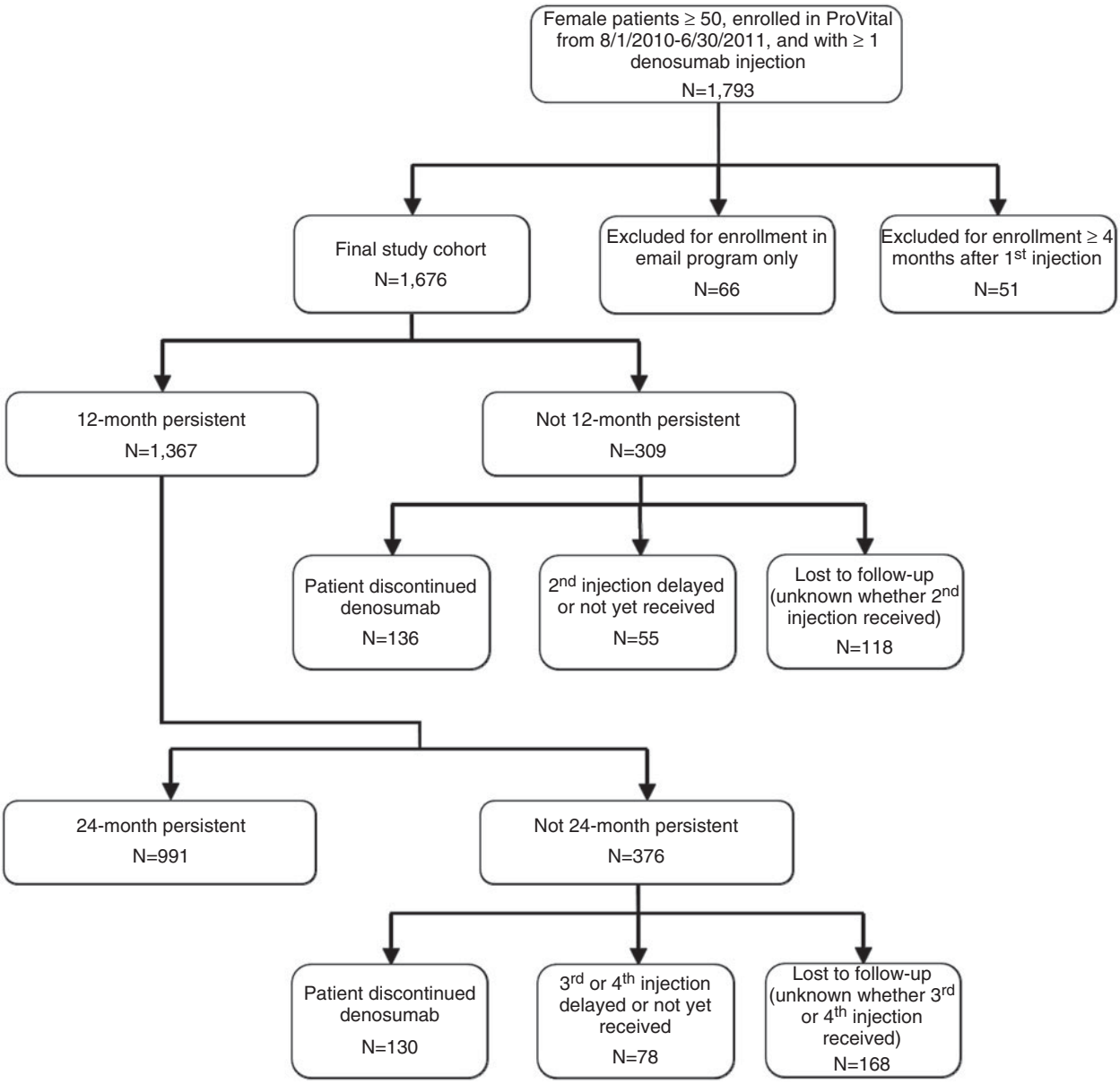

Figure 1. Patient flow diagram.

Results

Study sample and baseline characteristics

Initially, 1793 female patients >50 years of age were identified who were enrolled in the ProVital program from 1 August 2010 to 30 June 2011 and had ≥1 denosumab injection (Figure 1). Of the 1793 patients who met the inclusion criteria, 66 were excluded due to enrollment in the email program only, and another 51 patients were excluded due to enrollment ≥4 months after the first denosumab injection, resulting in a final sample size of 1676.

The mean age of patients in the study sample ($N = 1676$) was 73.7 years (ranging from 50 to 102 years) (Table 1). The mean weight of patients was 134.2 pounds (60.9 kg), and the mean height was 5.2 feet (158.5 cm). Most patients were from the provinces of Ontario (45.8%), Quebec (36.5%), and British Columbia (12.5%). 42.5% had a previous fracture, and 13.2% had a parent with a history of fracture. The majority of patients used calcium (89.2%) and vitamin D (94.4%). Half of the patients (51.4%) had private medication insurance, while 36.5% had public medication insurance. Approximately 70% of patients reported taking previous

Table 1. Baseline characteristics (patient reported).

	Study Cohort ($N=1676$) Mean (SD)
Age	73.7 (10.6)
Weight (lbs)[a]	134.2 (28.3)
Height (feet)[b]	5.2 (0.2)
	N (%)
Female Gender	1676 (100)
Province	
Alberta	29 (1.7)
British Columbia	210 (12.5)
Ontario	767 (45.8)
Quebec	611 (36.5)
Saskatchewan	38 (2.3)
Other	21 (1.3)
Previous Fracture	713 (42.5)
Parental History of Fracture	221 (13.2)
Current Smoker	128 (7.6)
Glucocorticoid Use	164 (9.8)
Has Arthritis	234 (14.0)
Has Secondary Osteoporosis	30 (1.8)
Alcohol (Consumes $\geq$3 units per day)	11 (0.7)
Calcium Use	1495 (89.2)
Vitamin D Use	1582 (94.4)
Medication Insurance Coverage	
Private	862 (51.4)
Private and Public	18 (1.1)
Public	612 (36.5)
None	97 (5.8)
Unknown	87 (5.2)
Had Previous Osteoporosis Treatment	1178 (70.3)
Previous Osteoporosis Treatments	
Zoledronic Acid (Aclasta)	108 (6.4)
Risedronate (Actonel)	634 (37.8)
Etidronate (Didronel)	65 (3.9)
Raloxifene (Evista)	68 (4.1)
Teriparatide (Forteo)	98 (5.9)
Alendronate (Fosamax)	520 (31.0)
Hormone Replacement Therapy	4 (0.2)
Drug name unknown	86 (5.1)

[a]Weight data available for a subset of patients ($N=1653$).
[b]Height data available for a subset of patients ($N=1655$).

PMO medications, the majority of which were risedronate (37.8%) and alendronate (31.0%).

Injection administration

Over half of the patients reported a change from the previous injection in the person administering the injection (57.6% from injection 1 to 2, 56.7% from injection 2 to 3, and 56.8% from injection 3 to 4).The first denosumab injection was most commonly given by a registered nurse in a specialist office (30.4%), a family or general practitioner physician (29.8%), or a specialist physician (21.2%) (Table 2). The second, third and fourth denosumab injections were given most commonly by a family or general practitioner physician (35.3%, 34.8%, and 38.6% respectively). The percentage of patients with an injection by a registered nurse in a specialist office was reduced over subsequent injections, and the percentage by a nurse at a different location increased. The average time between all injections was approximately 190 days, or 6.3 months.

Persistence with denosumab

Of the final sample, 1367 patients were persistent with their second injection of denosumab (12 month persistent) (Figure 1). Of the 309 patients in the study sample who were not 12 month persistent, 136 discontinued denosumab, 55 had a delayed second injection or had not yet received a second injection, and 118 were lost to follow-up. Of the 1367 patients who were 12 month persistent, 991 continued to be 24 month persistent and 376 were not 24 month persistent. Of the 376 patients who were not 24 month persistent, 138 discontinued denosumab, 78 had a delayed third or fourth injection or had not yet received a third or fourth injection, and 168 were lost to follow-up.

The 12 month persistence with denosumab was 81.6% (1367/1676 patients) with a 95% confidence interval (CI) of 79.6%, 83.4% (Table 3). The 24 month persistence with denosumab was 59.1% (991/1676 patients) with a 95% CI of 56.7%, 61.5%. The sensitivity analysis excluding patients who were lost to follow-up found that 87.7% of patients were 12 month persistent (1367/1558 patients), and 72.7% (991/1364) were 24 month persistent.

Delayed and discontinued injections

Out of the 136 patients without a second injection who discontinued denosumab by 12 months, adverse events were the most common reason for discontinuation (Table 4), cited by half (50.7%) of the patients. Other common reasons for discontinuation by 12 months included: the patient decided not to continue with therapy (19.1%), and the physician mandated that therapy be discontinued (11.8%).

Among the 138 patients who had a second injection but who discontinued denosumab by 24 months, adverse events were also the most common reason given for discontinuation (40.6%), followed by the patient decided not to continue with therapy (17.4%), the physician mandated that therapy be discontinued (9.4%), and death (9.4%).

A total of 179 patients provided reasons for delay of their denosumab injection, and patients could report more than one reason. Of the 286 reasons, physician postponed (16.0%), financial reasons (financial 10.6% and drug not covered 2.1%), and medical/dental procedures (11.7%) were reported most often.

Predictors of persistence

Figure 2 plots the odds ratio and 95% confidence interval (CI) for each predictor (independent variable), on a scale from 0 to 5, separately for 12 and 24 month persistence. Odds ratios greater than 1 indicate that the characteristic

Table 2. Person administering denosumab injections and length between injections.

	N (%)			
	First Injection (N = 1676)	Second Injection (N = 1419)	Third Injection (N = 1232)	Fourth Injection (N = 1065)
Person Administering Denosumab Injection				
Registered Nurse – Specialist Office	509 (30.4)	279 (19.7)	148 (12.0)	56 (5.3)
Pharmacy/Pharmacist	18 (1.1)	15 (1.1)	12 (1.0)	11 (1.0)
Physician – Family or General Practitioner	500 (29.8)	501 (35.3)	429 (34.8)	411 (38.6)
Physician – Specialist	355 (21.2)	220 (15.5)	239 (19.4)	180 (16.9)
Self	26 (1.6)	47 (3.3)	32 (2.6)	41 (3.9)
Registered Nurse – General Practitioner Office	143 (8.5)	156 (11.0)	112 (9.1)	68 (6.4)
Registered Nurse – Community Service Center	20 (1.2)	36 (2.5)	41 (3.3)	22 (2.1)
Registered Nurse – Other	85 (5.1)	133 (9.4)	138 (11.2)	142 (13.3)
Unknown	20 (1.2)	32 (2.3)	81 (6.6)	134 (12.6)
Days Since Previous Injection				
Mean		191.8	191.9	187.5
SD		48.3	39.2	26.1
Median		183.0	183.0	183.0
Min		120.0	120.0	102.0
Max		852.0	588.0	383.0

Table 3. Twelve month and 24 month persistence with denosumab.

	Persistent Patients		
	N (%)	Lower 95% CI	Upper 95% CI
Main Analysis (N = 1676 Total)			
12 Month Persistence[a]	1367 (81.6)	79.6	83.4
24 Month Persistence[b]	991 (59.1)	56.7	61.5
Sensitivity Analysis[c]			
12 Month Persistence (N = 1558 Total)	1367 (87.7)	86.0	89.3
24 Month Persistence (N = 1364 Total)	991 (72.7)	70.2	75.0

[a]Received at least two denosumab injections, and took each injection no more than 6 months plus 8 weeks (239 days) apart.
[b]Received at least four denosumab injections, and took each injection no more than 6 months plus 8 weeks (239 days) apart.
[c]Patients lost to follow-up were excluded.

Table 4. Reasons for discontinuation of denosumab.

	Patients who Discontinued	
	12 Months[a] (N = 136) N (%)	12 to 24 Months[b] (N = 138) N (%)
Reasons for Discontinuation		
Adverse Event	69 (50.7)	56 (40.6)
Patient Decided Not to Continue with Therapy	26 (19.1)	24 (17.4)
Physician Mandated	16 (11.8)	13 (9.4)
Change in Financial Status	5 (3.7)	3 (2.2)
Deceased	6 (4.4)	13 (9.4)
Financial	6 (4.4)	5 (3.6)
Switched Therapy (Unknown Therapy)	3 (2.2)	5 (3.6)
Switched Therapy to Zoledronic Acid (Aclasta)	1 (0.7)	4 (2.9)
Switched Therapy to Bisphosphonate	2 (1.5)	2 (1.5)
Switched Therapy to Teriparatide (Forteo)	0 (0.0)	2 (1.5)
Lack of Efficacy	1 (0.7)	0 (0.0)
Change in Insurance Coverage	1 (0.7)	1 (0.7)
Treatment Completed	0 (0.0)	10 (7.3)

[a]Percentage of patients without a second injection who report that they have discontinued denosumab (N = 136).
[b]Percentage of patients with a second injection but without a fourth injection who report that they have discontinued denosumab (N = 138, includes 8 patients who were counted in Figure 1 as not 12 month persistent due to a delayed second injection).

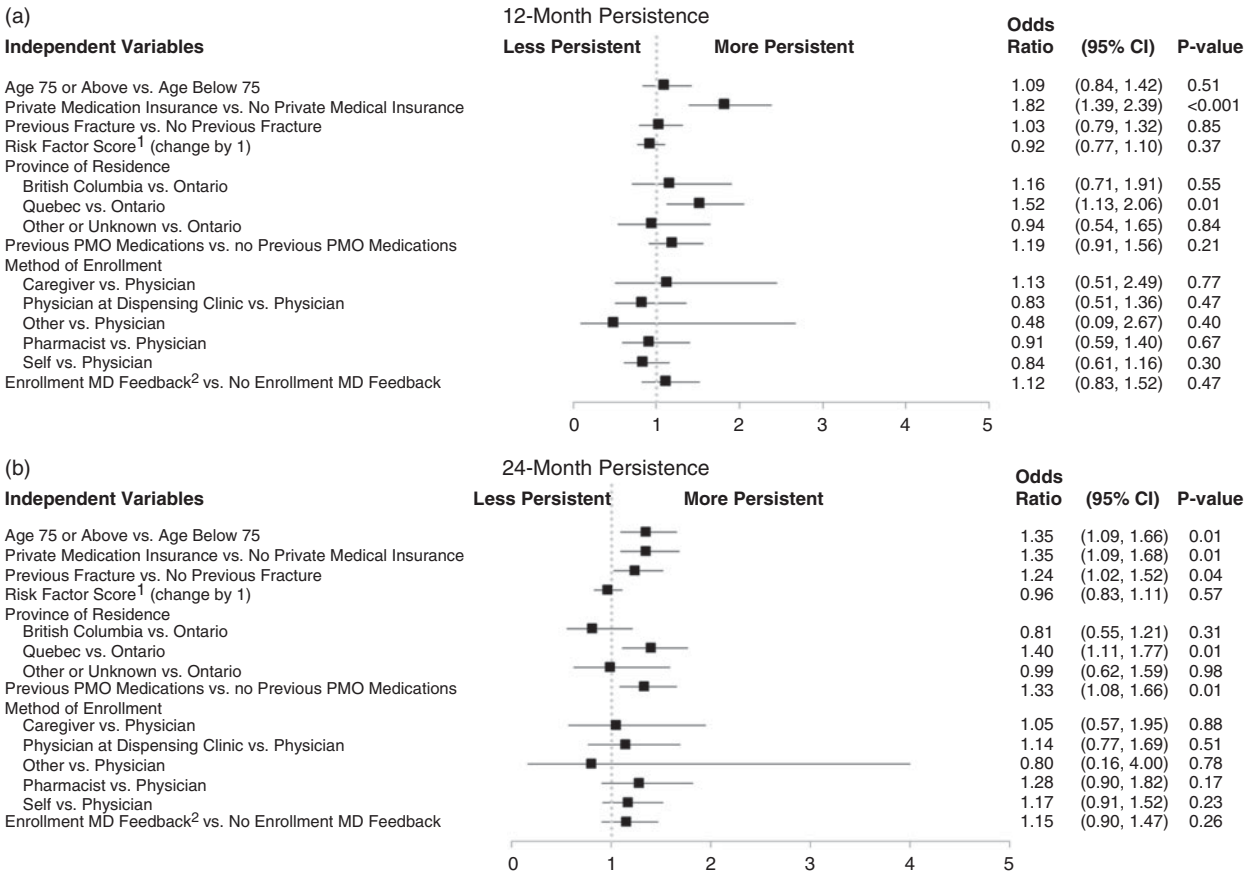

Figure 2. Logistic regression analysis of 12 and 24 month persistence with denosumab. [1]Risk score included the total count of parent with fracture, current smoker, glucocorticoids, rheumatoid arthritis, secondary osteoporosis, and alcohol (three or more units per day). Previous fracture was excluded from the risk score. [2]The physician has opted to receive summary adherence reports regarding treatment and next dose status for the patients. PMO: postmenopausal osteoporosis.

is associated with higher persistence, and odds ratios less than 1 indicate that the characteristic is associated with lower persistence. If the 95% CI line does not cross over the 1, then the association is statistically significant. Private medication insurance (odds ratio = 1.82, $p < 0.001$) and residing in Quebec (odds ratio = 1.52, $p = 0.01$) were both associated with higher 12 month persistence with denosumab (Figure 2a). In the sensitivity analysis (excluding patients lost to follow-up), private medication insurance remained a significant predictor of 12 month persistence with denosumab (odds ratio = 1.86, $p < 0.001$), but residing in Quebec was no longer significantly associated with denosumab persistence (odds ratio = 1.14, $p = 0.49$) (data not shown). Private medication insurance (odds ratio = 1.35, $p = 0.01$), residing in Quebec (odds ratio = 1.40, $p = 0.01$), age 75 or above (odds ratio = 1.35, $p = 0.01$), previous PMO medication use (odds ratio = 1.33, $p = 0.01$), and previous fracture (odds ratio = 1.24, $p = 0.04$) were all significantly associated with higher 24 month denosumab persistence (Figure 2b). In the sensitivity analysis, private medication insurance remained a significant predictor of 24 month persistence with denosumab (odds ratio = 1.41, $p = 0.01$), but previous fracture (odds ratio = 1.27, $p = 0.06$), residing in Quebec (odds ratio = 1.23, $p = 0.17$), age 75 or above (odds ratio = 0.98, $p = 0.87$), and previous PMO medication use (odds ratio = 1.15, $p = 0.30$) were no longer significantly associated with denosumab persistence (data not shown). In the sensitivity analysis, living in the province of British Columbia was associated with lower 24 month persistence (odds ratio = 0.60, $p = 0.03$).

Discussion

Our study provides results from a large sample of female patients enrolled in the Canadian ProVital support program between 1 August 2010 and 30 June 2011. This study sample is 5% of the total population of approximately 36,407 patients who were enrolled in the program as of October 2014[30], and the patients included in this study represent early users of denosumab in Canada. The 12 month persistence with denosumab was 81.6%, and

24 month persistence was 59.1%. To provide a conservative estimate of persistence, it was assumed that patients lost to follow-up were non-compliant. In a sensitivity analysis excluding patients lost to follow-up, 12 month and 24 month persistence were higher, at 87.7% and 72.7%, respectively. The high levels of persistence in this study may in part be related to selection bias incurred from self-enrollment into the program (for example, patients who enroll in the program may be more disposed to take medication as prescribed). Previous studies in osteoporosis have demonstrated that patient support programs may increase medication persistence[24,25,27].

As of December 2013, 78% of patients in the ProVital program were enrolled by physicians, 11% were enrolled by self/caregiver, 10% were enrolled by pharmacists, and 1% were enrolled through long-term care. Among the subset of patients enrolled into the program by physicians, approximately half were enrolled by general practitioners while the other half were enrolled by specialists (as of December 2013). However, earlier in the program two thirds of the patients who were enrolled by physicians were enrolled by specialists[30]. ProVital patients in our sample received their first injections primarily from registered nurses in a specialist office, family or general practitioner physician, or a specialist physician. After the first injection there was a shift from a nurse at a specialist office to nurses at different locations (for example, at a general practitioner office or a community service center), and to family or general practitioner physicians. Our results also found that the average time between subsequent injections was 6 months, as per prescribing recommendations[31].

Denosumab is the first subcutaneous treatment administered every 6 months for PMO. This route of administration and dosing interval has been associated with increased patient persistence and preference in the clinical trial setting[32,33]. The Denosumab Adherence Preference Satisfaction (DAPS) randomized crossover clinical trial reported higher persistence among denosumab users vs. bisphosphonate users (90.5% vs. 79.8% at 1 year; persistence with denosumab required receiving two injections, similar to our study)[33]. Similarly, another randomized clinical study comparing persistence among denosumab users vs. users of the oral bisphosphonate alendronate also found higher persistence among denosumab users during the first 12 months (89.7% vs. 79.8%)[34].

Limited research exists examining denosumab persistence in a real-world setting. A study by Karlsson *et al.* that used data from the Swedish National Prescription Register found that, of 2315 postmenopausal women initiating denosumab, 83% were persistent at 12 months and 62% at 24 months[35]. Karlsson *et al.* used a persistence definition that was similar to the one used in our study, and the 12 and 24 month persistence rates they reported are similar to what we found. However, Karlsson *et al.* did not indicate that they required patients to be enrolled in a patient support program. A prospective observational study by Silverman *et al.* of 935 patients receiving denosumab treatment in routine clinical practice in the US and Canada found that 82% of patients had 12 month persistence with denosumab (US, 79%; Canada 88%)[36]. Many of the Canadian patients in the Silverman *et al.* study were enrolled in the ProVital program (unpublished data). The results from Silverman *et al.* are also similar to what we found (and Silverman *et al.* also used the same persistence definition as ours). Using administrative claims data from Ontario, Canada, Burden *et al.* found that of 16,736 denosumab users, 55% persisted with therapy beyond the first year[37]. Due to differences in study design and patient inclusion criteria, it is difficult to directly compare this study to our results.

Previous studies have reported persistence with oral bisphosphonates in PMO. In these studies, estimates for 12 month persistence ranged from 54%–63%[38,39], which is lower than the 12 month persistence we report here for denosumab. Another study comparing 12 month persistence between oral bisphosphonates and intravenous bisphosphonates in PMO found slightly higher levels of persistence associated with intravenous bisphosphonates (for example, 66% for zoledronate); however, these levels are also lower than the 12 month persistence we report here for denosumab[40]. Similarly, the 24 month persistence we report here for denosumab (59.1%) is higher than a previous estimate for 24 month oral bisphosphonate persistence of 46%[39]. A retrospective study using a European registry of PMO patients found that persistence with the oral drug strontium ranelate was 80% at 1 year and 68% at 2 years, which is comparable to the persistence we observed here for denosumab[41].

Some previous studies have also evaluated persistence with osteoporosis drugs among patients enrolled in a support program. A recent study of persistence with teriparatide among PMO patients in an educational support program in Spain found 12 month persistence of 74.8% and 24 month persistence of 64.1%[42], which is similar to the levels of persistence we report here for denosumab. Another study in France of postmenopausal osteoporotic women who were enrolled in a patient education and follow-up program for teriparatide treatment reported that the persistence rate at 15 months was 81.5%[43]. A Dutch study found that 15.8% of patients in a community pharmacy intervention program discontinued osteoporosis medication after 1 year, compared with 27.8% of patients who were not in the program (nearly all patients in this study were treated with bisphosphonates)[44]. Persistence programs could offer patients an advantage by increasing communication between health care providers and patients, and providing reminders to patients. However, some conflicting results have been reported. A controlled trial in Malaysia found that a comprehensive

pharmaceutical care program did not improve persistence with bisphosphonates in postmenopausal osteoporotic women (12 month persistence was 89.8% in the control group and 87.0% in the intervention group)[45].

Predictors of persistence with denosumab included private medication insurance, residing in the province of Quebec, previous fracture, age 75 or above, and previous PMO medication use, and were all significantly associated with higher denosumab persistence (either at 12 or 24 months). Denosumab users may be at high risk for fracture or have failed or are intolerant to other PMO medications[31], and this profile may influence persistence. Residing in Quebec may be associated with persistence due to differences among provinces in drug coverage and reimbursement criteria. For example, denosumab was covered by the public drug plan in Quebec starting in February 2011, but was not covered by the public drug plan in Ontario until a year later, in February 2012[46,47]. Consistent with this interpretation, we observed that 12% of reasons given for delay of denosumab injection over the 24 months were financially related. Also, patients in Quebec have access to Local Community Services Centres, which provide additional patient follow-up/reminders independently of the ProVital program. In a previous study, baseline characteristics that showed significant associations with denosumab persistence in US patients included use of PMO medications >5 years before enrollment, lumbar spine bone mineral density (BMD) *T*-score, geographical region, physician gender, marital status and in Canada prior hip fracture[36]. Also, previous studies have reported that less frequent dosing, older age, presence of cardiovascular comorbidities, and prescription by a general practitioner (vs. other physician specialties) were positive determinants of persistence with other osteoporosis medications such as bisphosphonates, while dissatisfaction with therapy and side effects were negative determinants[48–50]. In our study we could not examine the association between adverse events and denosumab persistence because details of adverse events were not collected in the ProVital database. However, half of the patients in this sample who discontinued denosumab therapy cited adverse events as the reason, suggesting that this is an important factor affecting denosumab persistence. Discontinuation due to adverse events was similar in a persistence program for teriparatide (of patients who discontinued, 46.7% cited adverse events)[43]. Since obtaining regulatory approval to market, the benefit/risk profile of denosumab has remained positive for the approved indications.

A number of limitations should be considered when interpreting the results from this study. Data within the ProVital database was self-reported by patients and information was not confirmed by a physician. Persistence was based on the sample of patients enrolled in the program, and patient enrolment was voluntary. Therefore, there may be selection bias as patients who chose to enroll in the program may be different from a population who chose not to enroll in this program. For example, patients who chose to enroll in the program might be more likely to be persistent than patients who did not enroll into the program. Approximately one in four Canadian patients prescribed denosumab were enrolled in the program as of December 2013. Our study did not have a control group of patients who were not enrolled in a patient support program to determine whether the program influenced persistence, and results from this study may not be generalizable to a population receiving denosumab but not enrolled in a patient support program. As only denosumab was studied in this persistence program, direct comparisons could not be made regarding persistence with other drugs. Additionally, there are some limitations associated with the study inclusion criteria. Although patients in the program were assumed to have been diagnosed with osteoporosis because they were prescribed denosumab, the presence of an osteoporosis diagnosis was not verified.

In conclusion, 12 month persistence with denosumab was 81.6% and 24 month persistence was 59.1% among patients enrolled in the ProVital program. Persistence in this study was supported by reminders and support from the program. These rates of persistence are similar to those reported for patients taking denosumab in a Swedish claims database[35] and in a US and Canadian observational study[36], for patients enrolled in a patient education program taking teriparatide[42], for patients taking strontium ranelate in an observational study[41], and for patients taking bisphosphonates in a pharmaceutical care program[44]. However, the persistence rates in this study are higher than denosumab persistence rates reported in a claims database analysis in Canada[37], and are also higher than persistence levels reported from some real-world analyses for oral bisphosphonates[38,39]. The results from this study provide health care providers and decision makers with an improved understanding of real-world denosumab persistence patterns for patients enrolled in a support program in Canada.

Transparency

Declaration of funding

This study was sponsored by Amgen Canada Inc.

Declaration of financial/other relationships

M.A. has disclosed that he is an employee of and shareholder in Amgen. M.E. has disclosed that she is a former Amgen employee. V.W. and L.B. have disclosed that they are employees of Optum contracted by Amgen. A.P., A.K., W.B., D.K., and J.D.A. have disclosed that they have received research funding from Amgen. A.P., A.B., A.K., W.B., D.K., J.D.A., and F.T. have disclosed that they were consultants to Amgen. A.P., W.B., J.D.A., D.K., and F.T. have disclosed that they were speakers for Amgen. D.K.,

A.B., A.K., and F.T. have disclosed that they were advisors to Amgen. A.P., A.K., and D.K. have disclosed that they received honoraria from Amgen. A.P. has disclosed that she has received grants/research support from Eli Lilly and Merck; speakers bureau/honoraria from Eli Lilly and Merck; and consulting fees from Eli Lilly and Merck. J.D.A. has disclosed that he has been a consultant/speaker for Actavis, Eli Lilly, Merck, and Novartis; and conducted clinical trials for Eli Lilly, Merck, and Novartis.

CMRO peer reviewer 1 has disclosed that he is a recipient of consulting and advisory board fees from Servier, Novartis, Negma, Eli Lilly, Amgen, GlaxoSmithKline, Roche, Merck, Nycomed, NPS, Theramex and UCB. Peer reviewers 2 and 3 have no relevant financial or other relationships to disclose.

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