



Two-year persistence with teriparatide improved significantly after introduction of an educational and motivational support program

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Abstract

Summary This study evaluated the 2-year persistence with teriparatide in the Netherlands. Analyses showed that the risk of non-persistence was 28% lower in patients who were followed according to an additional educational and motivational support program.

Introduction Until recently, teriparatide (TPTD) was a third-line treatment option for severe osteoporosis in the Netherlands, which could only be prescribed by medical specialists based on a specific medical statement. We aimed to determine whether an educational and motivational support program (EMSP) increased 2-year treatment persistence with TPTD in patients with severe osteoporosis.

Methods We evaluated persistence in 1573 Dutch patients treated with TPTD from January 2013 until January 2018. From January 2013 onwards, all patients received a basic support program (BSP) consisting of an educational home visit to initiate TPTD treatment and phone calls (at 1, 2.5 and 8 weeks). Since May 2015, all patients received the EMSP consisting of the BSP extended with evaluation of medication adherence during phone calls, an additional phone call (at 12 months), and motivational letters at 9 and 14 months.

Results The EMSP showed a statistically significantly higher 2-year persistence (78%) with TPTD as compared with the BSP (72%). Reasons for treatment discontinuation were comparable between groups, except for the proportion of patients who had stopped TPTD administration due to side effects, which was significantly lower in the EMSP group (8% vs. 15% in BSP, $p < 0.001$). Overall, the risk of non-persistence was 28% lower in the EMSP compared with the BSP group (HR: 0.72; 95% CI: 0.55–0.93).

Conclusion The introduction of the EMSP has demonstrated to improve the persistence with TPTD, resulting in 78% of the patients being persistent with TPTD during the 2-year treatment period.

Keywords Educational program · Osteoporosis · Persistence · Support program · Teriparatide

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Introduction

Osteoporosis is a chronic skeletal disease characterised by decreased bone density and microarchitectural deterioration of normally mineralised bone, thus leading to an increase in fracture susceptibility [1]. In the Netherlands, it is estimated that 472,100 patients are diagnosed with osteoporosis, of whom 85% is female [2]. It is expected that the prevalence of osteoporosis will increase with 46% in the period between 2015 and 2040. The prevalence of patients diagnosed with osteoporosis is expected to be an underestimation because osteoporosis often does not involve any symptoms. Patients diagnosed with osteoporosis have an increased fracture risk. It is expected that the incidence of osteoporosis-related fractures from 2010 to 2030 will increase with 40% [3]. The most common fragility fractures are hip fractures, vertebral fractures and wrist fractures [3]. Mortality after an osteoporotic fracture is high: 25% of patients aged 55 years and older who sustain a hip fracture, die within 1 year after the fracture. Of the ones surviving, 50% remains permanently disabled leading to a decrease in quality of life. The main goal of treatment with anti-osteoporosis medication is to prevent fractures.

In the Netherlands, several treatment options for osteoporosis are available. According to the Dutch national clinical treatment guideline [4], oral bisphosphonates are the first-line treatment option, but persistence rates with oral bisphosphonates are reported to be low, with 1-year persistence of 45% [5–8]. Second-line treatment options are zoledronic acid and denosumab [4]. According to the clinical guideline, patients with severe osteoporosis, especially those with prevalent vertebral fractures, who have sustained a new fracture during treatment with anti-osteoporosis medication are eligible for treatment with teriparatide (TPTD), in the Netherlands a third-line treatment option. TPTD is an anabolic agent that stimulates osteoblastic bone formation to improve bone quality (improvement of trabecular connectivity and cortical bone thickness) and bone mass. In postmenopausal women, treatment of osteoporosis with TPTD decreased the risk of vertebral and non-vertebral fractures, and increased the spine, femoral neck and total hip BMD [9]. Moreover, in postmenopausal women, the risk of new vertebral and clinical fractures was significantly lower with TPTD compared with risedronate [10, 11]. In osteoporotic men, TPTD improved BMD and a reduced vertebral fracture risk [12]. To obtain maximal results from TPTD therapy, completion of the 2-year treatment period is required [13–15]. Relatively high persistence rates at 1 year have been previously reported for TPTD [16–18]; however, 2-year persistence rates were substantially lower [13, 14, 19]. Several follow-up support programs, who aimed to improve the patients' knowledge with respect to administration of TPTD and the importance of treatment completion of TPTD, have been developed to improve treatment persistence [20, 21].

In this retrospective cohort study, we aimed to assess whether an educational and motivational support program (EMSP)

increased 2-year treatment persistence with TPTD in patients with severe osteoporosis.

Patients and methods

Study design and population

In the Netherlands, only one central pharmacy is allowed to provide TPTD allowing a nationwide capture of patients. During our study period, TPTD was reimbursed for a maximum period of 24 months when prescribed by medical specialists to patients with severe osteoporosis, defined as having a third fracture during treatment with other anti-osteoporosis medication, while already having two prevalent vertebral fractures [22]. Because delivery of TPTD is provided by one central pharmacy, we were able to include all Dutch patients who were prescribed TPTD in an outpatient setting for the treatment of osteoporosis from January 2013 until January 2018. TPTD is provided as a pre-filled pen containing 750 mcg TPTD, which is administered to be used as a daily subcutaneous injection of 20 mcg TPTD for 28 consecutive days during a period of 24 months [22]. During this 24-month treatment period, patients received 26 pre-filled pens. In this study, all patients were followed from the start of TPTD treatment until the end of treatment with a maximal follow-up period of 2 years, nursing home admission (in that case, TPTD is no longer provided by the central pharmacy), or death.

Patient support programs

From January 2013 until May 2015, patients received a basic support program (BSP; Table 1), consisting of an intake telephone call, an educational home visit and regular telephone calls. During the intake, a staff member of the pharmacy collected information on the patient's comorbidities, allergies, previous use of TPTD and method of TPTD administration. Next, the first TPTD pen and an introduction kit were delivered by cold-chain delivery at the patient's home on an agreed date and time. After the delivery, an educational home visit was performed by a registered nurse to instruct patients on how to use TPTD, how to store TPTD, and to make patients aware of the importance of completing the full 24-month treatment period. Subsequently, patients received telephone calls by the same nurse at 1, 2.5 and 8 weeks after treatment initiation. These telephone calls were aimed to evaluate the patient's use of TPTD, to motivate the patient to complete the 24-month treatment period, and to answer potential questions.

From May 2015 onwards, all patients received the educational and motivational support program (EMSP; Table 1), which was developed to improve treatment persistence. During the intake phone call, a staff member of the pharmacy collected information on the patient's comorbidities, co-

Table 1 Content of support programs

| | Basic support program (BSP) (<i>N</i> = 649) | Basic support program + letters (BSP + letters) (<i>N</i> = 530) | Educational and motivational support program (EMSP) (<i>N</i> = 394) |
|-------------------------------------|--|--|--|
| Intake telephone call | + | + | + |
| Educational home visit | + | + | + |
| Telephone call | 1, 2.5 and 8 weeks | 1, 2.5 and 8 weeks | 1, 2.5 and 8 weeks, 12 months |
| Motivational letter | – | 9 and/or 14 months | 9 and 14 months |
| Medication adherence scoring tool | – | – | 2.5 and 8 weeks, 12 months |
| Additional phone call or home visit | – | – | + |

medications, allergies, height, weight, previous use of TPTD and method of TPTD administration. In addition to the BSP, the EMSP consists of an additional telephone call at 12 months. Also, the telephone calls at 2.5 weeks, 8 weeks and 12 months after treatment initiation were extended with a medication adherence scoring tool. The adherence scoring tool (Supplementary Table 1) is a questionnaire aimed to identify potential non-persistent patients and consists of two parts: one part to evaluate the patient's knowledge with respect to TPTD use, the other part to evaluate their motivation to complete the 24-month treatment period. Both parts contain three questions with a maximum subscore of 3 points per part. Depending on the subscores, or whenever nurse deemed it necessary, patients received an additional telephone call or home visit to improve their knowledge regarding to the use of TPTD and to enhance awareness of treatment completion. Finally, patients received two motivational letters: one at 9 months, the other at 14 months. These letters were aimed at motivating and encouraging the patients to complete the full treatment course by explaining them that TPTD increases bone formation and reduces the risk of subsequent fracture if the 2-year treatment course is completed. Further, the letter reminds patients that they can contact the pharmacy if they have questions regarding the treatment or that they can contact their physician if they are experiencing side effects of the treatment or are thinking about quitting the treatment. The letter is signed by the nurse who performed the intake visit and the telephone calls at 1, 2.5 and 8 weeks and 12 months.

In May 2015, the EMSP was introduced. At that time, the staff members of the pharmacy decided that the patients who received the BSP and were on treatment for 9 or 14 months

respectively, could benefit from the motivational letters which were part of the EMSP. So these patients were instructed and followed according to the BSP program and received one or two motivational letters; therefore, this group was labelled as the BSP + letters group (Table 1). To allow for a fair comparison between the three support programs, all patients of whom treatment was initiated between February 2014 and April 2015 were included in this group.

TPTD delivery and persistence

In principle, the patients received 10 deliveries of TPTD: at the first delivery, one pen was delivered, the following deliveries consisted of three pens and the last delivery consisted of one pen. If the patient wanted to receive more pens (maximum 6) or fewer pens at each delivery, the schedule was adjusted to the patient's preferences. The staff members of the pharmacy called the patients if a new delivery had to be scheduled. By exception, patients could receive a new pen if it was broken or put in the freezer instead of the refrigerator. The patients did not return the empty pens to the pharmacy.

Persistence was defined as the act of continuing treatment for the prescribed duration without exceeding the permissible gap [23]. For this study, TPTD persistence was calculated using delivery dates and the number of pens delivered per delivery. For each delivery, a permissible gap was calculated as a gap of 28 days plus extra days TPTD from the previous delivery. Thus, for example when a patient received a new pen while still having TPTD for 2 days in the old pen, a permissible gap of 30 days was used (2 days from the old pen + 28 days from the new pen). In addition, patients were classified as persistent if they had received a minimum of 24 pens because every pen contained more TPTD than necessary for the prescribed 28 days of treatment per pen. So, if a patient used the pen until it was completely empty, 24 pens were sufficient to complete the 24-month treatment course.

Data collection

Data were collected from the pharmacy's database including sex, age, weight, height, comorbidities and the method of TPTD administration (self-administration, administration by a family member or by a home care nurse). Further, dates and reasons for additional phone calls or home visits (on request of the patient or based on the score of the medication adherence scoring tool) were registered. In addition to the reasons for treatment discontinuation, adverse events related to TPTD use were also registered from December 2013 onwards.

Statistical analysis

Patients were followed from the start of TPTD treatment until the end of treatment, nursing home admission (in that case, TPTD was no longer provided by the central pharmacy) or

death. Treatment persistence was analysed using age- and sex-adjusted Cox proportional hazard models. In addition, the Cox proportional hazard model was adjusted for the TPTD administration (by patient himself vs. family members or home care), as it might influence the persistence. Data analyses were performed with SAS version 9.42.

Results

In total, 1573 patients were included of whom 649 patients were instructed and treated according to the BSP, 530 patients according to the BSP + letters and 394 patients according to the EMSP. In Table 2, the baseline characteristics are shown.

Table 2 Baseline characteristics of all patients treated with teriparatide according to the different support programs

| | BSP | | BSP + letters | | EMSP | |
|--------------------------------------|-----------|--------|---------------|--------|-----------|--------|
| | (N = 649) | | (N = 530) | | (N = 394) | |
| | N | (%) | N | (%) | N | (%) |
| Number of women | 568 | (87.5) | 469 | (88.5) | 333 | (84.5) |
| Age (mean, SD) | 72.0 | (10.0) | 72.2 | (10.0) | 72.1 | (8.9) |
| Weight in kg (mean, SD) ^a | | | 65.7 | (14.7) | 65.3 | (13.3) |
| Height in m (mean, SD) ^b | | | 1.6 | (0.1) | 1.6 | (0.1) |
| BMI (mean, SD) ^c | | | 24.8 | (4.8) | 24.6 | (4.5) |
| Medical history ^d | | | | | | |
| Diabetes | | | 21 | (4.0) | 20 | (5.1) |
| Hypertension | | | 102 | (19.2) | 115 | (29.2) |
| Depression | | | 42 | (7.9) | 35 | (8.9) |
| Liver disease | | | 6 | (1.1) | 10 | (2.5) |
| Kidney disease | | | 12 | (2.3) | 6 | (1.5) |
| Heart failure | | | 43 | (8.1) | 54 | (13.7) |
| Epilepsy | | | 11 | (2.1) | 10 | (2.5) |
| Method of TPTD administration | | | | | | |
| Self-injecting | 609 | (93.8) | 484 | (91.3) | 350 | (88.8) |
| Home care | 22 | (3.4) | 33 | (6.2) | 33 | (8.4) |
| Family member | 11 | (1.7) | 9 | (1.7) | 8 | (2.0) |

BSP, basic support program

EMSP, educational and motivational support program

^a Weight was missing for all patients who were enrolled in the BSP, in 238 who were enrolled in the BSP + letters and for 74 patients who were enrolled in the EMSP

^b Height was missing for all patients who were enrolled in the BSP, who were enrolled in 240 in the BSP + letters and for 75 who were enrolled patients in the EMSP

^c BMI was missing for all patients who were enrolled in the BSP, in 242 who were enrolled in the BSP + letters and 76 patients who were enrolled in the EMSP

^d Data regarding medical history was only available for patients who were enrolled in the BSP + letters and the EMSP

Two-year persistence was 71.6% in the BSP group and 78.4% in the EMSP group ($p < 0.001$) (Table 3, Fig. 1). Based on the medication adherence scoring tool, in total, 42 additional phone calls or home visits were conducted in the EMSP. The reasons for treatment discontinuation were comparable between the three groups, except for the discontinuation according to the side effects of TPTD use which was significantly lower in the EMSP group as compared with the BSP group (7.6% vs. 14.6%, respectively, p value = 0.014). Two-year persistence with TPTD in patients who received the BSP + letters was 73.8% vs. 71.6% in the BSP group (Table 3, Fig. 1).

Age- and sex-adjusted Cox regression analysis showed that the risk of non-persistence was 28% lower in the EMSP group as compared with the BSP group (HR: 0.72; 95% CI: 0.55–0.93). Instructing and following patients according to the BSP + letters program did not reduce the risk of non-persistence (HR: 0.90; 95% CI: 0.72–1.13). Because there was a difference in the way of administering TPTD in the different groups, the analysis was additionally adjusted for the method of TPTD administration, resulting in the same significant lower risk of non-persistence (HR: 0.72; 95% CI: 0.56–0.94). Among women, the risk of non-persistence was 32% lower with the EMSP as compared with the BSP (HR: 0.68; 95% CI: 0.52–0.92), while in men there was no difference in the risk of non-persistence between the EMSP and BSP. Furthermore, in patients aged 70–79 years, the risk of non-persistence was 44% lower with the EMSP as compared with the BSP (HR: 0.56; 95% CI: 0.36–0.88).

Discussion

We found that 2-year persistence with TPTD was significantly higher (78.4%) in the EMSP group as compared with the BSP group (71.6%). The proportion of patients who stopped taking

Table 3 Two-year persistence according to gender and age categories and reasons for treatment discontinuation

| | BSP | | BSP + letters | | EMSP | |
|---------------------------------------|-----------|--------|---------------|--------|-----------|---------|
| | (N = 649) | | (N = 530) | | (N = 394) | |
| | N | (%) | N | (%) | N | (%) |
| Persistent patients | 465 | (71.6) | 391 | (73.8) | 309 | (78.4)* |
| < 70 years | 66 | (28.0) | 46 | (24.6) | 29 | (19.3) |
| 70–79 years | 69 | (28.2) | 55 | (26.1) | 26 | (17.3) |
| > 80 years | 49 | (29.2) | 38 | (28.8) | 30 | (32.2) |
| Reasons for treatment discontinuation | | | | | | |
| Side effects of TPTD use | 95 | (14.6) | 64 | (12.1) | 30 | (7.6)* |
| Advised by physician | 29 | (4.5) | 29 | (5.5) | 17 | (4.3) |
| Non-persistent dispensing | 37 | (5.7) | 31 | (5.8) | 26 | (6.6) |
| Other reasons | 23 | (3.5) | 15 | (2.8) | 12 | (3.0) |

* $P < 0.05$ vs. BSP

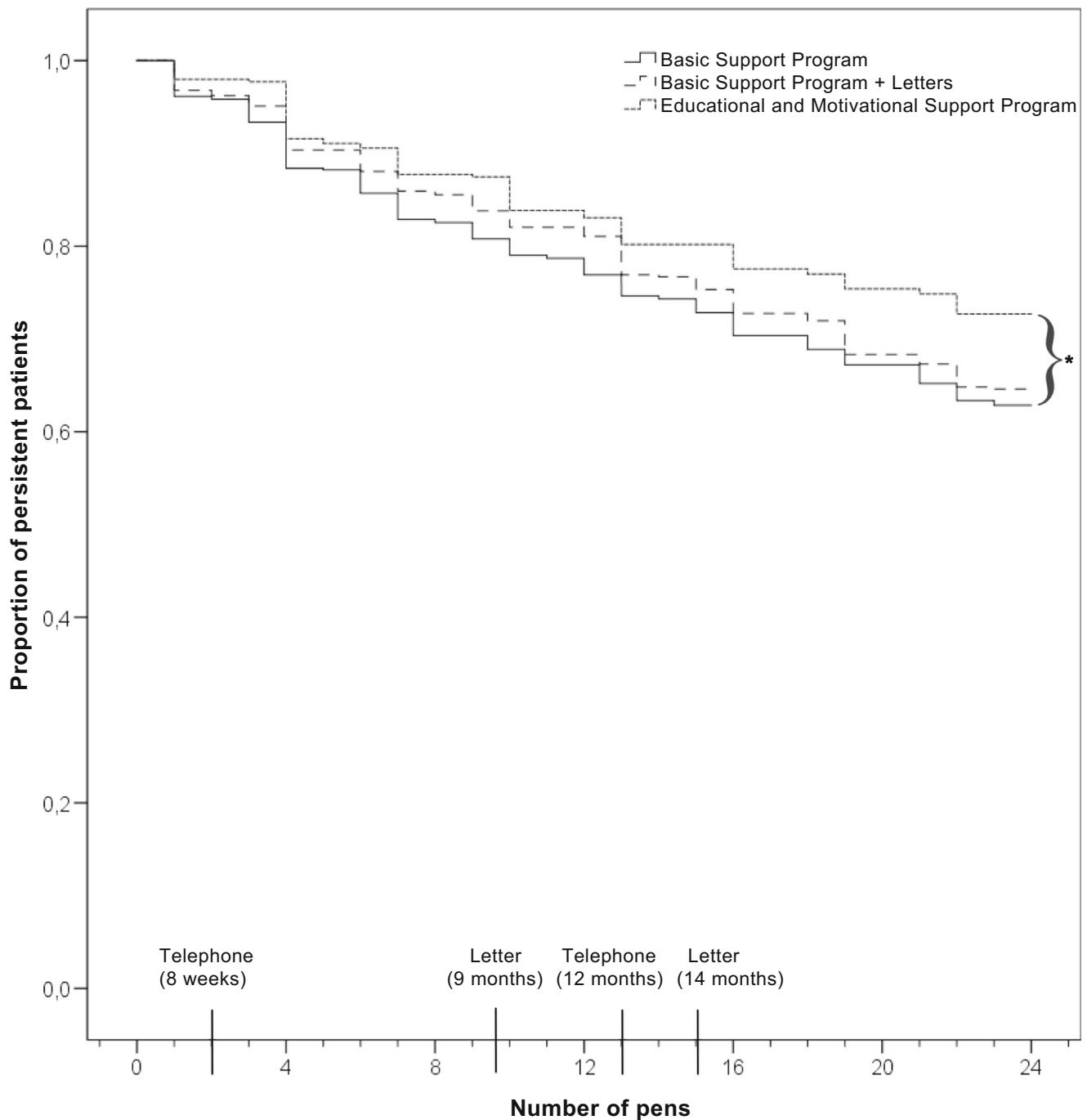


Fig. 1 Persistence with teriparatide according to the different support programs

TPTD due to side effects was significantly lower in the EMSP group as compared with the BSP group. Patients instructed and followed according to the EMSP had a 28% lower risk of non-persistence during the 24-month treatment compared with patients instructed and followed according to the BSP.

Remarkably, the 24-month persistence rates of the BSP and EMSP group in our study were higher compared with the rates reported by others, ranging from 12.1 to 61.4% [13, 14, 19]. In previous studies, persistence rates were calculated based on data from health care claims databases [13, 14] or dispensing

data [19], which is quite different from our study because patients in our study are selected based on specific criteria of severe osteoporosis and can only access TPTD by a medical declaration of the treating medical specialist. The findings in our study may also reflect that our BSP program, consisting of a treatment initiation visit and phone calls at 1, 2.5 and 8 weeks after treatment initiation, was associated with a relatively high persistence. Strikingly, we were able to show that an additional support according to the EMSP leads to even a further increase in persistence.

High persistence rates were previously observed when TPTD was administered within monitoring programs, with 1-year persistence rates of 75 and 87% [18, 24], a 15-month persistence rate of 82% [20], an 18-month persistence rate of 79% [18] and 2-year persistence rates of 69% [24]. In 2-year follow-up study of Nogues et al. [24], patient satisfaction with an educational support program consisting of 22 phone calls in 24 months was evaluated. As like in our study, the proportion of patients who discontinued their treatment due to side effects was significantly lower in patients who received the education and follow-up program. This emphasises that patient selection, full reimbursement of the medication and an organised follow-up system attribute to treatment persistence of TPTD. Tamone et al. [25] reported statistically significantly different 18-month persistence rates of 86% and 78%, respectively in an intervention group with a follow-up program and non-intervention group, which is in line with the findings of our study. Our study, however, was focused on the 2-year persistence which was slightly lower with 71.6% in the BSP group and 78.4% in the EMSP group. We showed that the development of a specific medication adherence scoring tool aiming at identification of potential non-persistence with focused additional telephone calls or home visits to improve knowledge regarding how to use TPTD and to enhance awareness of treatment completion significantly reduces the risk of patients to discontinuing TPTD treatment due to side effects with 28%. Even in the context of an existing monitoring program (BSP), this finding shows that specific attention to identify factors that attribute to potential non-persistence increases persistence to the full 2-year treatment period of TPTD, which is very important given the severe osteoporosis of these patients [15]. The identification of patients who might have a knowledge gap with respect to side effects is probably the most important determinant of improving persistence. These patients were provided with additional information to increase their knowledge and possible side effects were addressed and discussed with them either during an additional phone call or during home visit. Previous studies have shown that treatment of osteoporosis with TPTD or other anabolic agents is more expensive than treatment with alendronate or risedronate [26, 27]. To the best of our knowledge, the cost-effectiveness of patient support programs for improving persistence with TPTD has not been published previously. Given the efficacy of TPTD in high-risk patients, as described in the VERO trial [10, 11], and taking into the higher costs of TPTD treatment compared with other anti-osteoporosis treatments, it may be of additional value to implement a patient support program (including telephone calls, letters and home visits from a dedicated nurse) in order to optimise persistence with TPTD.

Our study has several limitations and strengths. First, it was not a randomised study but an evaluation of regular care monitoring programs. Due to the changes in the intake telephone visit, we did not have data regarding the medical history, weight and height of patients whose treatment was initiated during the BSP and BSP + letters group. Second, systematic registration

of the side effects was initiated from December 2013 onwards. Therefore, we were unable to identify if there was a difference in the type and/or severity of the reported side effects according to the different support programs. Third, the medication adherence scoring tool was developed by the employees of the pharmacy. To develop the scoring tool, the staff reviewed several already available medication adherence scoring tools and evaluated if the scoring tools were able to identify patients with a knowledge gap or patients who needed additional motivation in order to optimise adherence [28, 29]. Based on their review, they concluded that none of the scoring tools was able to meet their needs and matched with the additional interventions (e.g. an intervention aimed at improving knowledge by an additional phone call or home visit from a nurse; and an intervention to improve motivation by a home visit from a nurse trained in motivational interviewing). Because the medication adherence scoring tool was a part of the regular care of the pharmacy, it immediately was implemented in the care process and not validated in a study. Fourth, we were not able to study the cost-effectiveness of the EMSP versus the BSP because we did not have fracture data before. The strength of our study is that we were able to evaluate persistence in all patients who were prescribed TPTD in the Netherlands from January 2013 until January 2018 because TPTD was provided by one central pharmacy. Hence, delivery date, number of deliveries and number of delivered pens used to calculate persistence were well registered. Further, the study was based on real-life data of patients with severe osteoporosis with previous fractures who are at high subsequent fracture risk. The finding that the 2-year persistence rate could be improved by almost 10 to 78% might be clinically relevant for optimal treatment of high-risk osteoporotic patients, especially because there was a 28% lower risk of TPTD discontinuation because of side effects.

In summary, real-life persistence with TPTD during the 24-month treatment course of patients with severe osteoporosis was significantly higher after introduction of a patient support program to identify and provide additional information to patients who may have a knowledge gap with respect to side effects, mainly due to a 28% lower risk of TPTD discontinuation because of side effects.

Compliance with ethical standards

Conflicts of interest Maud van Maren has no disclosures.

Caroline E. Wyers has no disclosures.

Johanna H.M. Driessen has no disclosures.

Jonathan V. Visser is employed at ApotheekZorg. ApotheekZorg receives financial support from Eli Lilly Nederland B.V. to perform the patient support program and to fund this study.

Frank de Vries supervises two PhD students who are employed by F. Hoffmann La Roche Ltd. (Basel, Switzerland and Welwyn Garden City, UK). The topics of these PhDs are not related to the current study manuscript and he has not received any fees or reimbursements for this.

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