Turk J Phys Med Rehab 2020;66(3):262-270
DOI: 10.5606/tftrd.2020.4114
Available online at www.turkishjournalpmr.com

Original Article

Evaluation of pain, quality of life, and patient satisfaction in parenterally treated patients with postmenopausal osteoporosis

Tuğba Özsoy-Ünübol[1], Gülseren Akyüz[2], Samaya Mirzayeva[2], Tuba Güler[3]

[1]Department of Physical Medicine and Rehabilitation, Sultan Abdülhamid Han Training and Research Hospital, Istanbul, Turkey
[2]Department of Physical Medicine and Rehabilitation, Marmara University Faculty of Medicine, Istanbul, Turkey
[3]Department of Physical Medicine and Rehabilitation, Ankara Numune Training and Research Hospital, Ankara, Turkey

Received: December 24, 2018 **Accepted:** May 20, 2019 **Published online:** February 26, 2020

ABSTRACT

Objectives: This study aims to evaluate pain, quality of life, and patient satisfaction in parenterally treated patients with postmenopausal osteoporosis (OP).

Patients and methods: Between May 2016 and January 2018, a total of 138 patients (mean age 63.78 years; range, 50 to 70 years) with postmenopausal OP were retrospectively analyzed. All patients were previously treated with denosumab (DEN) and parenteral forms of bisphosphonates such as zoledronic acid (ZOL) and ibandronate (IBN). The pain severity was evaluated using the Visual Analog Scale (VAS) and Brief Pain Inventory-Short Form (BPI-SF). The quality of life was evaluated using the Quality of Life Questionnaire of the European Foundation for Osteoporosis (Qualeffo-41). For the evaluation of patient satisfaction, a three-item questionnaire including satisfaction with the medication, route, and frequency of administration was applied.

Results: Of the patients, 50 received DEN, 48 received ZOL, and 40 received IBN treatment. There was no significant difference in any of the pain parameters. All domains of the Qualeffo-41 were similar among the three groups. The patients in the DEN group were more satisfied with their medication (DEN: 88%, ZOL: 43.75%, and IBN: 52.5%), its administration route (DEN: 84%, ZOL: 43.8%, and IBN: 57.5%), and the frequency of its administration (DEN: 84%, ZOL: 56.25%, and IBN: 52.5%) (p=0.0001).

Conclusion: Neither of the medication showed a superior effect on quality of life. However, patients were more satisfied with medications used in a six-month interval and applied subcutaneously. Of these three treatment options, DEN seems to be a step ahead in terms of patient satisfaction.

Keywords: Osteoporosis, pain, patient satisfaction, quality of life, treatment.

Osteoporosis (OP) is a common disease which affects the bone mass, structure, and strength and that results in an increased risk of fragility fracture.[1] The disease itself and its associated complications have an adverse impact on the patients' physical, mental, social, and emotional health and lead to a drop in the quality of life (QoL).[2,3] Fractures and the fear of fractures may cause restricted mobility, decreased independence in activities of daily living, and social isolation.[4] As a consequence, pain and QoL evaluation play an important role in the evaluation and follow-up of patients.

The medications used in the treatment of OP can be classified into two groups: anti-resorptive agents such as bisphosphonates or denosumab (DEN) which inhibit bone destruction, and anabolic agents such as teriparatide which stimulate bone formation. Among anti-resorptive agents, bisphosphonates, which have been widely used for years, have oral and intravenous forms. On the other hand, DEN is a human recombinant monoclonal antibody, which is a relatively new agent administered subcutaneously.[1]

Corresponding author: Gülseren Akyüz, MD. Marmara Üniversitesi Tıp Fakültesi, Pendik Egitim ve Araştırma Hastanesi, Fiziksel Tıp ve Rehabilitasyon Anabilim Dalı, 34899 Kaynarca, Pendik, İstanbul, Türkiye. e-mail: gulserena@gmail.com

Cite this article as:
Özsoy-Ünübol T, Akyüz G, Mirzayeva S, Güler T. Evaluation of pain, quality of life, and patient satisfaction in parenterally treated patients with postmenopausal osteoporosis. Turk J Phys Med Rehab 2020;66(3):262-270.

Early results of the study was presented as a poster at 12th ISPRM World Congress July 8-12, 2018, Paris, France.

There are many studies evaluating QoL and pain in patients with OP and, for the most part, these patients were compared with healthy groups.[5-8] In a study comparing zoledronic acid (ZOL) with alendronate (ALN) in terms of QoL and patients' preference, the patients preferred ZOL, although there was no significant difference in terms of QoL.[9] Eskiyurt et al.[10] also examined patients' preferences regarding monthly ibandronate (IBN). Among patients with postmenopausal OP who previously received daily/weekly ALN or risedronate, the patients preferred monthly IBN and they were more satisfied and compliant with the treatment. There are also several studies evaluating the patient satisfaction and compliance in patients treated with DEN and ALN.[11,12]

However, there is a limited number of comparative studies investigating QoL, medication satisfaction, and patient preferences in parenterally treated patients.[13] In the present study, therefore, we aimed to evaluate pain, QoL, and patient satisfaction in patients with postmenopausal OP receiving DEN and parenteral bisphosphonates ZOL, and IBN.

PATIENTS AND METHODS

Between May 2016 and January 2018, a total of 138 patients (mean age 63.78 years; range, 50 to 70 years) with postmenopausal OP who were admitted to the Marmara University Faculty of Medicine, Physical Medicine and Rehabilitation outpatient clinics were retrospectively analyzed using the hospital records. All patients were previously treated with denosumab (DEN) and parenteral forms of bisphosphonates such as zoledronic acid (ZOL) and IBN. *Inclusion criteria were as follows:* being aged 50 to 70 years, having postmenopausal OP, receiving the same medications regularly for at least 24 months in parenteral forms (DEN, ZOL, and IBN), being able to read and write fluently in Turkish, and giving a informed consent. Those with secondary OP, metabolic bone diseases other than OP (e.g. Paget's disease or renal osteodystrophy), bone metastasis and hypogonadism, acute vertebral or non-vertebral fractures, and illiterate patients were excluded. In addition, patients with a history of treatment with parenteral forms (intravenous IBN, ZOL, DEN and teriparatide) and those treated with parenteral forms for more than three years were also excluded from the study. A written informed consent was obtained from each patient. The study protocol was approved by the Marmara University School of Medicine Ethics Committee (06.05.2016-09.2016.291). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The patients were divided into three groups according to their type of medication. Their demographic data such as age, body mass index (BMI), and educational status were recorded. Bone mineral density (BMD) was assessed using the dual-energy X-ray absorptiometry (DXA) via a Lunar DPX-L instrument (Lunar Radiation Corp., Madison, WI, USA). The patients with a T score of -2.5 standard deviation (SD) and below were defined as having OP, between -1 and -2.5 SD as having osteopenia (low bone density), and -1 SD and above as normal.[14] The L1-L4 and femur neck T scores within the last year were recorded. The clinical risk factors of OP were questioned, and the 10-year risks of major osteoporotic and hip fracture were calculated according to the Fracture Risk Assessment Tool (FRAX).[15,16] All patients' dorsal and lumbar anteroposterior and lateral radiographs were examined to determine vertebral compression fractures.

All eligible patients were invited to the hospital for an evaluation of pain, QoL, and patient satisfaction. All questionnaires were given to the patients via face-to-face interviews. Dorsal and lumbar back pain were investigated with the Visual Analog Scale (VAS). In addition, a nine-item, Brief Pain Inventory-Short Form (BPI-SF), which has a valid and reliable form in Turkish, was applied to evaluate pain severity and the impact of pain on daily functions.[17] For a pain severity evaluation, the BPI-SF has four items including the "worst and least pain in the last 24 h," "pain on average", and "pain right now." The pain severity score is the arithmetic mean of these four items. The pain interference evaluation consists of seven items as follows: general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. The arithmetic mean of these seven items is used as a pain interference score.

For the evaluation of QoL, we used a 41-item Quality of Life Questionnaire of the European Foundation for Osteoporosis (Qualeffo-41), which has a valid and reliable form in Turkish.[18] The Qualeffo-41 consists of five domains including pain (5 items), physical function (17 items), social function (7 items), general health perception (3 items), and mental function (9 items). In total, the lowest possible score is 0, and the highest possible score is 100. Higher scores reflect a lower QoL. To assess medication satisfaction, a three-item questionnaire, including the satisfaction with the medication, the route and the frequency of administration, was applied. A five-point Likert-type

TABLE 1
Baseline sociodemographic and clinical characteristics of patients

	DEN (n=50)				ZOL (n=48)				IBN (n=40)				
	n	%	Mean±SD	Median	n	%	Mean±SD	Median	n	%	Mean±SD	Median	*p*
Age (year)			65.2±7.9	65			63.4±8.6	64			62.5±9.7	62	0.316*
Body mass index (kg/m^2)			27.2±5.3	26.3			26.6±5.6	26.4			26.0±4.4	25.6	0.540*
Education level													0.946†
Primary-Middle School	35	70			34	70.8			26	65			
High School	8	16			7	14.6			6	15			
College-University	7	14			7	14.6			8	20			
BMD (L1-L4) T score			-2.7±0.9	-2.6			-2.8±0.9	-2.9			-2.6±0.5	-2.7	0.204‡
BMD (femur neck) T score			-1.9±0.8	-2.0			-2.0±0.9	-2.2			-1.9±0.7	-1.9	0.839*
History of non-vertebral fracture													0.079†
Yes	18				8				9				
No	32				40				31				
Parents' hip fracture history													0.758†
Yes	5				3				4				
No	45				45				36				
Smoker													0.662†
Yes	4				6				3				
No	46				42				37				
Vertebral compression fracture													0.825†
Yes	11				9				7				
No	39				39				33				
FRAX major osteoporotic fracture risk			11.8±8.3	8.7			9.6±5.7	8.6			9.2±6.6	7.2	0.193‡
FRAX hip fracture risk			4.3±5.3	2.7			3.6±3.6	2.6			3.1±3.8	1.8	0.302
Menopause duration (year)			14.6±7.2	15			12.9±7.2	12.5			12.5±8.1	10	0.265‡
Number of medication administration			4.9±1.0	5			2.4±0.5	2			9.3±1.2	9	-

DEN: Denosumab; ZOL: Zoledronic acid; IBN: Ibandronate; SD: Standard deviation; * ANOVA test; † Chi-square test; ‡ Kruskal-Wallis test; BMD: Bone mineral density.

TABLE 2
Pain parameters according to medications used

	DEN (n=50)			ZOL (n=48)			IBN (n=40)			
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
Lumbar back pain VAS (0-10)			2.4±2.5			3.5±2.3			3.2±2.4	0.055*
Dorsal back pain VAS (0-10)			2.5±2.5			3.3±2.6			2.6±2.5	0.263*
BPI pain severity score (0-10)			3.0±1.9			3.6±1.8			3.8±1.5	0.096*
BPI pain interference score (0-10)			2.3±2.4			2.9±1.9			3.0±1.6	0.093*
BPI pain										0.210†
None	10	20		5	10.41		2	5		
Vertebral	17	34		18	37.5		12	30		
Non-vertebral	10	20		6	12.5		7	17.5		
Vertebral and non-vertebral	13	26		19	39.58		19	47.5		

DEN: Denosumab; ZOL: Zoledronic acid; IBN: Ibandronate; SD: Standard deviation; * Kruskal-Wallis test; † Chi-square test; VAS: Visual Analog Scale; BPI: Brief Pain Inventory-Short Form.

scale with descriptive choices ranging from "strongly disagree to strongly agree" was used to measure and compare the satisfaction levels between the DEN, ZOL, and IBN patients.[13]

As the parenteral treatments of the patients were administered in our hospitals, all patients were observed during and after the administration for side effects and complications. Before and after the treatment, all patients' vital signs (i.e., blood pressure, body temperature, pulse, and respiration rate) were checked and recorded to their files. During the interviews, all patients were questioned about any side effects of the medication they experienced.

Statistical analysis

Power analysis was performed using the G*Power version 3.1.9.2 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). In terms of patient satisfaction, the study power was 86% at an alpha level of 0.05. Statistical analysis was performed using the PASW version 17.0 software (SPSS Inc., Chicago, IL, USA). The normality of the parameters was assessed with the Kolmogorov-Smirnov test. Descriptive data were expressed in mean ± standard deviation (SD), median (min-max), and number and frequency. The Student's t-test and analysis of variance (ANOVA) were used to compare the parameters in each group showing normal distribution. The Mann-Whitney U and Kruskal-Wallis test were used to compare the parameters in each group showing non-normally distribution. For comparison of categorical data, the chi-square test was used. The Spearman correlation analysis was used to evaluate the correlation between the pain parameters and QoL. A p value of <0.05 was considered statistically significant with 95% confidence interval (CI).

TABLE 3
Pain and quality of life parameters according to presence of vertebral fractures

	Vertebral fracture		
	Yes (n=27)	No (n=111)	
	Mean±SD	Mean±SD	*p*
Lumbar back pain VAS (0-10)	3.0±2.4	2.9±2.6	0.8851*
Dorsal back pain VAS (0-10)	3.1±2.5	2.8±2.6	0.5341*
BPI pain severity score (0-10)	3.5±1.8	3.4±1.8	0.8811*
BPI pain interference score (0-10)	2.8±2.1	2.7±2.0	0.7771*
Qualeffo-41 pain (0-100)	32.4±27.5	29.5±26.0	0.6551*
Qualeffo-41 physical function (0-100)	37.1±18.4	26.9±17.8	0.0091*
Qualeffo-41 social function (0-100)	63.7±18.8	54.6±25.9	0.1741*
Qualeffo-41 general health perception (0-100)	58.7±16.0	50.7±18.3	0.0601*
Qualeffo-41 mental function (0-100)	44.6±14.1	38.0±13.7	0.0292†
Qualeffo-41 total (0-100)	42.5±14.3	35.9±14.0	0.0322†

SD: Standard deviation; * Mann-Whitney U test; † Student's t-test; VAS: Visual Analog Scale; BPI: Brief Pain Inventory-Short Form; Qualeffo-41: Quality of Life Questionnaire of the European Foundation for Osteoporosis.

TABLE 4
Qualeffo-41 results of patients

	DEN (n=50)	ZOL (n=48)	IBN (n=40)	
	Mean±SD	Mean±SD	Mean±SD	*p*
Pain (0-100)	24.7±23.2	35.4±27.6	30.5±27.1	0.127*
Physical function (0-100)	27.2±18.4	30.5±20.2	28.6±16.1	0.682*
Social function (0-100)	53.9±29.8	58.3±21.2	55.8±23.6	0.684*
General health perception (0-100)	49.5±16.0	51.5±16.8	56.2±21.7	0.209*
Mental function (0-100)	38.8±16.6	36.9±10.6	42.5±13.8	0.171†
Total (0-100)	34.7±15.2	38.6±13.9	38.2±13.7	0.337†

DEN: Denosumab; ZOL: Zoledronic acid; IBN: Ibandronate; SD: Standard deviation; * Kruskal-Wallis test; † ANOVA test.

RESULTS

Of a total of 138 patients with postmenopausal OP included in this study, 50 were using DEN, 48 were using ZOL, and 40 were using intravenous IBN. There was no significant difference in the baseline demographic characteristics among the groups (p>0.05) (Table 1).

The patients were evaluated for pain using the VAS and BPI-SF which showed no significant differences in the pain scores (p>0.05) (Table 2). When the pain scores were analyzed categorically as "having pain" (VAS ≥1) or "not having pain", lumbar back pain was reported in 56% of the DEN group, 75% of the ZOL group, and 75% of the IBN group. Dorsal back pain was also reported in 56% of the DEN group, 68.8% of the ZOL group, and 60% of the IBN group. In patients with a vertebral fracture, the patients' pain scores were higher and their QoL was more impaired. However, there was a statistically significant difference only in the physical function scores, mental function scores, and total scores of the Qualeffo-41 (Table 3).

Medications were assessed according to pain, physical function, social function, general health perception, mental function domain, and the total scores of the Qualeffo-41. There was no significant difference among the groups (p>0.05), (Table 4).

The correlations between the pain measurements and QoL were analyzed using the Spearman test. All pain parameters showed a significant correlation with every domain of the Qualeffo-41. Although the VAS scores showed a weak-to-moderate correlation with the Qualeffo-41 scores, the pain severity and interference scores of the BPI-SF were strongly correlated with the total scores of the Qualeffo-41 (Table 5).

In terms of overall patient satisfaction according to the medication used, 62% of patients in the DEN group, 41.7% of patients in the ZOL group, and 50% of patients in the IBN group answered with "agree." Similarly, 60% of the DEN group, 37.5% of the ZOL group, and 55% of the IBN group were agreed that they were satisfied with the administration routes of their medications, while 54% of the DEN group, 45.8% of the

TABLE 5
Correlations of pain parameters with quality of life

	Pain	Physical function	Social function	General health perception	Mental function	Total
BPI pain severity						
r	0.651**	0.562**	0.379**	0.459**	0.343**	0.643**
p	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
BPI pain interference						
r	0.487**	0.625**	0.371**	0.500**	0.212*	0.648**
p	0.0001	0.0001	0.0001	0.0001	0.012	0.0001
Lumbar back pain VAS						
r	0.370**	0.332**	0.350**	0.270**	0.153	0.371**
p	0.0001	0.0001	0.0001	0.001	0.073	0.0001
Dorsal back pain VAS						
r	0.661**	0.419**	0.236**	0.316**	0.204*	0.474**
p	0.0001	0.0001	0.002	0.0001	0.016	0.0001

Spearman correlation analysis; * Correlation was significant at 0.05 level; ** Correlation was significant at 0.01 level; BPI: Brief pain inventory; VAS: Visual Analog Scale.

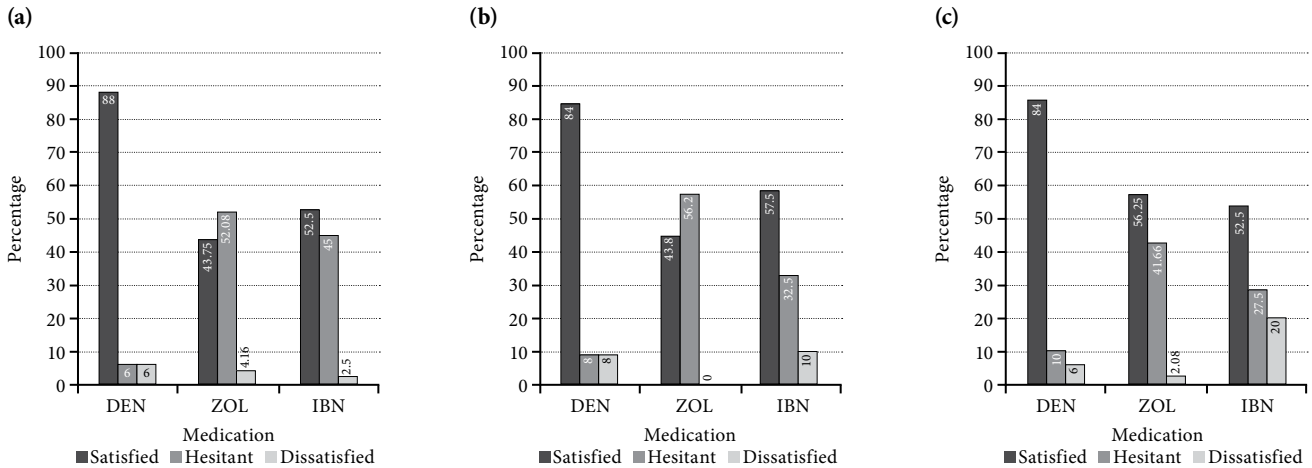

Figure 1. Patient satisfaction rates according to medication, route and frequency of administration. **(a)** Satisfied with the medication (overall). **(b)** Satisfied with the route of the administration. **(c)** Satisfied with the frequency of the administration.
DEN: Denosumab; ZOL: Zoledronic acid; IBN: Ibandronate.

ZOL group, and 45% of the IBN group agreed that they were satisfied with the frequency that their medications were administered. For the statistical analysis, the chi-square test was initially used; however, it turned out to be inappropriate due to the small numbers of cells. As such, a regrouping of the answer types was performed. The answers of "strongly disagree" and "disagree" were regrouped as "dissatisfied," the answer of "neither agree or disagree" remained the same, but named as "hesitant", and "strongly agree," and "agree" were regrouped as "satisfied." According to these categorizations, the patients who received DEN were significantly more satisfied than those who received IBN and ZOL (p=0.0001), (Figure 1).

Prior to treatment, a slightly high blood pressure was reported in three of 40 patients in the IBN group and in four of 48 patients in the ZOL group. After high blood pressure was controlled, the medications were administered. Following infusion, 52% (25/48) of the patients who had ZOL infusions and 37.5% (15/40) of the patients who had IBN infusions showed signs of fatigue, malaise, or myalgia. Paracetamol was used to relieve these symptoms. No patients who were treated with DEN experienced any of these side effects.

DISCUSSION

Many factors affect QoL in patients with OP, such as age, comorbidity, mobility, and fractures, particularly in the hip or vertebrae.[19,20] In this study, we evaluated pain, QoL, and patient satisfaction with the parenteral medications they were administered. Our study results showed no significant differences in the baseline demographic and clinical data of the patients and in pain, which was assessed using the VAS and BPI-SF. The QoL was evaluated using an OP-specific Qualeffo-41 questionnaire which yielded no significant difference in any domain of the questionnaire or total scores for each group. However, correlation analysis revealed a significant correlation between all pain parameters and all domains of the Qualeffeo-41.

Pain in OP can be acute or chronic. Acute pain is typically associated with fractures, and chronic pain may be linked to disturbances in the entire musculoskeletal system. Although there are limited data about the pathogenesis of pain in OP, it is primarily composed of three mechanisms of increased osteoclastic activity, peripheral sensitization, and central sensitization.[2] To provide homogeneity, this study excluded patients with acute pain. Chronic lumbar back pain affected 56% of the patients in the DEN group and 75% of the patients in both the ZOL and IBN groups (VAS ≥1). Dorsal back pain affected 56% of the DEN group, 68.8% of the ZOL group, and 60% of the IBN group. There were no significant differences in any of the pain evaluation. In a study comparing the prevalence of low back pain in individuals with and without OP, 48.6% of the patients with OP suffered from low back pain.[21] In another study evaluating the prevalence of comorbidities in OP, the second most common comorbidity was found to be chronic low back pain with a prevalence of 49.6%.[22] As the aforementioned studies were prevalence studies, however, they did not report mean or median pain

scores.[21,22] In the current study, the estimated prevalence of low back pain was higher, and the mean VAS scores for low back pain ranged from 2.40 to 3.52, which is considered mild. In the Basaran et al.'s[23] study on the effects of vitamin D on the QoL of Turkish women with OP, the women were questioned about their back pain using the VAS (0-100). The mean VAS score was found to be 30.4, which is similar to the mean VAS score of the present study.

While there are many studies comparing QoL among OP patients, osteopenic patients, and healthy controls, these studies have produced conflicting results.[5,8,24] In the Bączyk et al.'s[24] study comparing QoL in patients with osteopenia, postmenopausal OP, and normal BMD, patients with normal BMD reported significantly better QoL.[24] In contrast, in the Pamuk et al.'s[5] study of QoL in postmenopausal women with and without OP, a negative correlation between BMD values and QoL was found. In another study of patients with postmenopausal OP, osteopenia, and normal BMD values, no significant differences were identified in the QoL among the groups.[8] Of note, this study included OP patients without vertebral and non-vertebral fractures and who only received vitamin D and calcium for medical treatment over the past two years. When Hadji et al.[9] investigated the efficacy of ZOL and ALN on QoL, they showed an improvement in QoL after one year, but found no significant difference between the groups. In a prospective, multicenter study, the QoL was assessed in patients with postmenopausal OP who were treated with weekly and monthly oral bisphosphonates.[25] The study included patients who were treated with weekly ALN or risedronate for at least six months prior to enrolment. All patients were switched from weekly bisphosphonates to monthly IBNs without a wash-out period. The QoL was assessed at baseline and six months after the switch. At the end of the study, the patients' QoL improved six months after the switch. In the current study, the QoL scores for all the treatment groups were found to be similar. Neither of the medication had a superior effect on QoL. However, due to its cross-sectional design, it is impossible to conclude which medication affected the QoL more.

Many studies have previously investigated the effects of vertebral fractures on QoL.[19,26,27] Vertebral fractures affect physical, mental, social factors and influence the patients' psychological status such as anxiety or depression.[28] Several studies have also shown that OP without fractures can negatively affect the QoL.[20,29] Therefore, the present study compared pain and QoL in patients with and without vertebral fractures. Although the study's parameters were negatively influenced by the presence of fractures, statistically significant differences were only found in the physical function, mental function, and total scores of the Qualeffo-41. Pain has been shown to have a negative impact on QoL, and OP itself and pain are associated with emotional, social, and mental problems.[2,3] In the current study, we found a significant correlation between the QoL and pain, and the pain parameters were positively correlated with all domains of the Qualeffo-41, indicating worse QoL with increased pain severity.

It has been demonstrated that treatment satisfaction is associated with an increased risk of medication discontinuation.[30] Several studies have also shown that compliance and persistence are typically low in OP patients who take oral bisphosphonates.[31,32] This low compliance is often caused by the gastroesophageal side effects of the medication and the weekly/monthly usage periods.[33-35] These compliance issues may make it necessary to change the medication's administration route in selected cases.[35] According to the patients' preferences, satisfaction degree, and complaints in patients receiving DEN and ALN, significantly favorable results have been obtained with DEN.[11,12] In the Fraenkel et al.'s[36] study of medication preferences, the authors found that the route of administration strongly affected the decision of the patient. Therefore, in the current study, we attempted to compare parenteral forms with each other to provide homogeneity, resulting in a higher ratio of patients who were satisfied with their medication in the DEN group (88%) than in the other groups (43.75% and 52.5%). In addition, the DEN group showed a higher rate of satisfaction with the route of administration (84%) than the groups receiving intravenous medication (43.8% and 57.5%). In a cross-European discrete-choice experimental study for anti-OP treatment, the patients from every country were reported to prefer six-monthly subcutaneous injections.[37] Similar to these findings, the present study also found that the DEN group (six-month interval) was more satisfied with the frequency of medication than the ZOL group (one-year interval) and the IBN group (three-month interval).

Side effects can also affect patient satisfaction and QoL. In their study, Modi et al.[38] showed that gastrointestinal side effects adversely affected QoL and patient satisfaction with treatment. In the

current study, all patients were observed for side effects and complications before, during, and after the administration of medication. Prior to the administration of medication, blood pressure was slightly elevated in three of 40 patients receiving IBN and in four of 48 patients receiving ZOL. No similar effect was identified in the DEN group. As the intravenous administration of medication can cause anxiety in certain patients, which can increase blood pressure, in turn, subcutaneous administration may currently be superior to intravenous administration. Nonetheless, there is still a need for further large-scale studies including patients who are suitably selected to test this hypothesis.

After the administration of medication, 25 of 48 patients who had ZOL and 15 of 40 patients using IBN experienced fatigue, malaise, or myalgia. However, none of the patients who were treated with DEN complained about these side effects. According to a study of the safety profiles of the intravenous bisphosphonates (ZOL and IBN) and the rates in which patients showed influenza-like symptoms, such as myalgia, arthralgia, fever, and headache, these symptoms were found in 54.3% of the ZOL patient group and in 33.1% of the IBN patient group.[39] The current study reported similar rates for the occurrence of those symptoms. In a study by Sheedy et al.,[13] 29% of ZOL patients had flu-like symptoms, while these symptoms were not present in any patient who was administered DEN. These finding are consistent with the results of the present study.

Nonetheless, this study has some limitations. First, the treatment effectiveness was unable to be evaluated due to its cross-sectional design. In addition, Turkey has certain requirements for reimbursements associated with DEN. Accordingly, patients need to have been unresponsive to oral bisphosphonate therapy or unable to tolerate oral bisphosphonates before the use of DEN. Therefore, all patients who used DEN needed to have been treated with oral bisphosphonates. The current Turkey's reimbursement requirements for DEN, thus, make it impossible to select bisphosphonate-naïve patients. On the other hand, the main strength of the present study is that it was able to evaluate patients through face-to-face interviews. All medications, including DEN, were administered in the hospital setting and, to the best of our knowledge, this study is the first to compare these medications for pain, QoL, and patient satisfaction.

In conclusion, none of the medications were found to be superior to one another in terms of QoL. In addition, patient satisfaction was most influenced by side effects and the route and frequency of administration. The patients were also more satisfied with medication which was administered in a six-month interval and with subcutaneous administration. However, further blinded, randomized-controlled studies are required to evaluate both treatment efficacy and patient satisfaction in the long-term.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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