DOI: 10.4274/tod.29491

Open, Prospective, Multi-Center, Two-Part Study of Patient Preference with Monthly Ibandronate Therapy in Women with Postmenopausal Osteoporosis Switched From Daily or Weekly Alendronate or Risendronate-BONCURE: Results of Turkish Sub-Study

Günlük veya Haftalık Alendronat veya Risendronat Alan Postmenopozal Osteoporozlu Kadınlarda Aylık İbandronat İçin Hasta Tercihinin Değerlendirildiği Açık-Etiketli, Prospektif, Çok-Merkezi, İki-Aşamalı Çalışma-BONCURE: Türkiye Alt-Çalışması

Nurten Eskiyurt, Jale İrdesel*, Vesile Sepici**, Hatice Uğurlu, Yeşim Kirazlı****, Füsun Ardıç*****, Bülent Bütün******, Gülseren Akyüz*******, Lale Cerrahoğlu********, Ömer Faruk Şendur*********, Peyman Yalçın**********, Sema Öncel**********, Merih Sarıdoğan**********, Tunay Sarpel**********, Mehmet Tosun**********, Yeşim Gökçe Kutsal**********, Kazım Şenel**********, Savaş Gürsoy**********, Ferhan Cantürk**********, Hüseyin Demir**********, Fatih Özdener**********, Hakan Öncel**********; BONCURE Study Group***

Istanbul University Istanbul School of Medicine, Department of Physical Medicine and Rehabilitation, Istanbul, Turkey
**Uludag University School of Medicine, Department of Physical Medicine and Rehabilitation, Bursa, Turkey*
***Gazi University School of Medicine, Department of Physical Medicine and Rehabilitation, Ankara, Turkey*
****Selcuk University School of Medicine, Department of Physical Medicine and Rehabilitation, Konya, Turkey*
*****Ege University School of Medicine, Department of Physical Medicine and Rehabilitation, Izmir, Turkey*
******Pamukkale University School of Medicine, Department of Physical Medicine and Rehabilitation, Denizli, Turkey*
*******Akdeniz University School of Medicine, Department of Physical Medicine and Rehabilitation, Antalya, Turkey*
********Marmara University School of Medicine, Department of Physical Medicine and Rehabilitation, Istanbul, Turkey*
*********Celal Bayar University School of Medicine, Department of Physical Medicine and Rehabilitation, Manisa, Turkey*
**********Adnan Menderes University School of Medicine, Department of Physical Medicine and Rehabilitation, Aydin, Turkey*
***********Ankara University School of Medicine, Department of Physical Medicine and Rehabilitation, Ankara, Turkey*
************Dokuz Eylul University School of Medicine, Department of Physical Medicine and Rehabilitation, Izmir, Turkey*
*************Istanbul University Cerrahpasa School of Medicine, Department of Physical Medicine and Rehabilitation, Istanbul, Turkey*
**************Cukurova University School of Medicine, Department of Physical Medicine and Rehabilitation, Adana, Turkey*
***************Karadeniz Technical University School of Medicine, Department of Physical Medicine and Rehabilitation, Trabzon, Turkey*
****************Hacettepe University School of Medicine, Department of Physical Medicine and Rehabilitation, Ankara, Turkey*
*****************Ataturk University School of Medicine, Department of Physical Medicine and Rehabilitation, Erzurum, Turkey*
******************Gaziantep University School of Medicine, Department of Physical Medicine and Rehabilitation, Gaziantep, Turkey*
*******************Ondokuz Mayis University School of Medicine, Department of Physical Medicine and Rehabilitation, Samsun, Turkey*
********************Erciyes University School of Medicine, Department of Physical Medicine and Rehabilitation, Kayseri, Turkey*
*********************Roche Pharmaceuticals, Istanbul, Turkey*

Summary

Aim: BONCURE (Bonviva for Current Bisphosphonate Users Regional European Trial), aimed to evaluate patient preference with monthly ibandronate in women with postmenopausal osteoporosis who previously received daily or weekly alendronate or risendronate.
Materials and Methods: This prospective, open-label study consisted of two sequential stages, Part A (screening) and Part B (treatment). Patients enrolled into Part A completed the Candidate Identification Questionnaire (CIQ). In Part B, after completing the Osteoporosis Patient Satisfaction Questionnaire (OPSAT-Q), patients received monthly oral ibandronate 150 mg for 6 months. Following treatment, patients completed the OPSAT-Q and Preference Questionnaire.
Results: A total of 223 patients (mean age, 63.7±9.51 years) were enrolled in Part A from Turkey. Among them, 103 (46.2%) answered "YES" to at least one CIQ question. The mean composite OPSAT-Q domain scores increased for convenience (mean change, 15.3±17.7 points), quality of life (10.4±20.4 points), overall satisfaction (11.9±22.7 points), and side effects (3.3±18.8 points). At month 6, 177 subjects (92.7%) preferred once-monthly dosing schedule and 99.0% were compliant (≥80%) with study treatment. Thirty (15.6%) subjects experienced mild to moderate adverse events, mostly gastrointestinal.
Conclusion: Postmenopausal women with osteoporosis prefer and are more satisfied and compliant with monthly dosing of ibandronate than daily or weekly bisphosphonate treatment. (Turkish Journal of Osteoporosis 2012;18:1-7)
Key words: Bisphosphonate, ibandronate, postmenopausal osteoporosis, patient preference

Address for Correspondence/Yazışma Adresi: Nurten Eskiyurt MD, İstanbul University İstanbul School of Medicine, Department of Physical Medicine and Rehabilitation, İstanbul, Turkey
Phone: +90 212 635 11 85 GSM: +90 542 257 11 26 E-mail: eskiyurt@istanbul.edu.tr **Received/Geliş Tarihi:** 18.01.2012 **Accepted/Kabul Tarihi:** 20.04.2012
Turkish Journal of Osteoporosis, published by Galenos Publishing./Türk Osteoporoz Dergisi, Galenos Yayınevi tarafından basılmıştır.

Özet

Amaç: BONCURE (Mevcut Bisfosfonat Kullanıcıları İçin Bonviva Bölgesel Avrupa Çalışması) ile daha önce günlük veya haftalık alendronat veya risendronat alan postmenopozal osteoporozu olan kadınlarda aylık ibandronat için hasta tercihinin değerlendirilmesi amaçlandı.
Gereç ve Yöntemler: Bu prospektif, açık-etiketli çalışma, iki ardışık aşamadan oluşmuştur: A (tarama) ve B (tedavi) aşaması. A aşamasına kaydolan hastalar Aday Kimlik Anketi (CIQ) tamamladı. B aşamasında, Osteoporoz Hasta Memnuniyeti Anketi (OPSAT Q) tamamladıktan sonra, hastalar 6 ay boyunca aylık oral 150 mg ibandronat aldı. Tedaviden sonra, hastalar OPSAT-Q ve Tercihi Anketi tamamladı.
Bulgular: Türkiye'den 223 hasta (yaş ortalaması 63,7±9,51) A aşamasına dahil edildi. Bunların arasında, 103'ü (%46,2) en az bir CIQ sorusunu "EVET" yanıtladı. Ortalama bileşik OPSAT-Q alan puanları; kolaylık (ortalama değişiklik, 15,3±17,7 puan), yaşam kalitesi (10,4±20,4 puan), genel memnuniyet (11,9±22,7 puan) ve yan etkiler (3,3±18,8 puan) için arttı. Altıncı ayda 177 hasta (%92,7) bir kez aylık doz programını tercih etti ve %99,0'u çalışma tedavisi ile uyumlu (≥%80) idi. Otuz hasta (%15,6) çoğunlukla gastrointestinal olan hafif ve orta şiddette advers olay yaşadı.
Sonuç: Postmenopozal osteoporozu olan kadınlar, günlük veya haftalık bifosfonat tedavisine göre aylık ibandronatı daha çok tercih etmekte ve bu tedavi ile daha memnun ve uyumlu olmaktadır. (Türk Osteoporoz Dergisi 2012;18:1-7)
Anahtar kelimeler: Bifosfonat, ibandronat, postmenopozal osteoporoz, hasta tercihi

Introduction

Osteoporosis is a major public health issue affecting one in three postmenopausal women (1,2). Currently, bisphosphonates are considered to be the 'gold standard' for the treatment of postmenopausal osteoporosis. Bisphosphonates decrease the incidence of vertebral and nonvertebral fractures, increase bone mass, and normalize bone turnover to premenopausal levels (3,4). However, bisphosphonates have complex dosing instructions and side effects, which limit their clinical utility (5,6). Therefore, patient compliance and persistence with long-term therapy are main obstacles of bisphosphonate treatment. It has been shown that 47% of postmenopausal women on oral bisphosphonate had suboptimal adherence at 6 months (7).

Dose frequency of bisphosphonates is traditionally decreased for patients to comply with long-term therapy (8,9). Reducing the frequency of the intake of oral bisphosphonates may beneficially impact the attitude of patients towards compliance and further persistence (10). It is known that the reduction of daily dose frequency is associated with better adherence, patient compliance, greater efficacy, higher quality of life, and patient satisfaction in chronic diseases (8,11). Less frequent dosing with weekly and monthly oral regimens of bisphosphonates are generally preferred by patients over daily dosing (12,13). Currently, monthly bisphosphonate dosing regimens that increased patients' preference and adherence over weekly regimens are treatment of choice for bisphosponates (14,15).

Ibandronate is the first nitrogen-containing oral bisphosphonate for osteoporosis that can be administered in a monthly regimen. In a Phase III study, oral ibandronate both as daily and intermittent dosing regimens showed significant bone mineral density increases and reduction in the risk of vertebral fractures, compared to placebo (16). The MOBILE study showed that monthly oral administration of 100 mg and 150 mg ibandronate regimens were as effective as 2.5 mg daily oral ibandronate and well tolerated (17,18). In the recent studies, patients previously using weekly bisphosphonates (alendronate) reported improved satisfaction and preference with monthly ibandronate dosing (19-21).

To collect further regional data on preference of patients for different dosing regimens of bisphosphonates, BONCURE (Bonviva for Current Bisphosphonate Users Regional European Trial) study evaluated the patients' satisfaction, preference and compliance, and tolerability of monthly ibandronate 150 mg in women with postmenopausal osteoporosis who had previously received weekly or daily alendronate or risedronate by using a validated satisfaction instrument relevant to treatment for osteoporosis (Osteoporosis Patient Satisfaction Questionnaire, OPSAT-Q). This report represents the results of the BONCURE study for the Turkish sub-population.

Materials and Methods

Overall study design and study population

This was a prospective, open-label, multicenter, international study consisting of two sequential stages, Part A (screening) and Part B (treatment) on postmenopausal women. The study was conducted in 43 centers from Croatia, Bosnia&Herzegovina, Macedonia, Albania, Turkey, Serbia. This report represents the results of 223 patients whose data are submitted from 20 sites in Turkey. All postmenopausal women, who had applied to the outpatient clinics at the study sites receiving once-daily or once-weekly alendronate or risedronate for the treatment or prevention of osteoporosis for a minimum of 3 months, and were able to understand and willing to comply with the study treatment requirements were enrolled into Part A of the study. Patients enrolled into Part A completed the Candidate Identification Questionnaire (CIQ) and among them those willing to comply with the protocol requirements, not hypersensitive to bisphosphonates, be able to stand or sit upright for at least 60 min, and without any medical condition or concomitant medication that could influence the study results or represent a safety hazard for the patient were enrolled to Part B of the study.

In Part B, patients completed the OPSAT-Q and received monthly oral biphosphonate therapy (ibandronate 150 mg once-monthly, Bonviva® 150 mg, Roche, Istanbul, Turkey) for 6 months. The patients completed the OPSAT-Q and Preference Questionnaire (Pref-Q), and provided a blood sample for laboratory safety tests at baseline assessment. Monthly ibandronate dosing was started one week after the last weekly bisphosphonate dose (with a window of up to 7 days). All patients were instructed to take supplemental calcium and vitamin D for the full duration of the study.

All participants provided written informed consent before participating in the Part A and Part B of the study. The study was approved by the institutional ethics committees of each study center and conducted in accordance with the latest version of Declaration of Helsinki.

Study Assessment Tools

Candidate Identification Questionnaire (CIQ)

CIQ was completed by all of the subjects enrolled to Part A to determine the tendency for general preference of dosing schedule, previous gastrointestinal side effects and compliance to previous osteoporosis medication. In the CIQ, patients were asked to answer either 'yes' or 'no' to the following 3 questions: (1) "I would prefer a monthly oral dosing schedule to my current (daily or weekly) dosing schedule", (2) "More than once per month, I have experienced stomach upset within 48 hours of taking my osteoporosis medication", (3) "Over the past 3 months, I have missed taking 3 or more doses of my current (daily or weekly) osteoporosis medication".

Osteoporosis Patients Satisfaction Questionnaire (OPSAT-Q)

The OPSAT-Q is a validated questionnaire designed to capture satisfaction with bisphosphonate treatment (22). It comprises 16 questions and four domains: convenience (questions 1–6), quality of life (questions 7 and 8), overall satisfaction (questions 9 and 10), and side effects (questions 11–16). All items were scored such that higher scores represented greater satisfaction or less bother and frequency of side effects. Treatment satisfaction was measured with the OPSAT-Q composite satisfaction score (OPSAT-Q CSS), which was the average of the scores from the four domains of the OPSAT-Q converted to a 0–100-point scale.

Preference Questionnaire (Pref-Q)

All patients were asked to answer the Pref-Q at the end of the study (month 6) to define their preference for either monthly ibandronate or daily or weekly alendronate or risedronate.

Study end-points

The primary end-point was the proportion of current daily or weekly bisphosphonate users who answer "YES" to any of the questions in the CIQ for Part A of the study and the proportion of patients who report preference for either monthly ibandronate or daily or weekly alendronate or risedronate for Part B of the study. For safety evaluation, physical examination and laboratory tests findings, adverse events and concomitant medications were recorded throughout the study.

Statistical Analysis

The primary endpoint of Part A study was analyzed on all of the patients enrolled into collected from Part A. The study endpoints collected from Part B were analyzed in three analysis population: intent-to-treat (ITT) population which included all patients who received at least one dose of study medication, per protocol (PP) population which excluded all patients in the ITT population who significantly violated the study protocol, and safety analysis population which included all patients who received a dose of study medication and had at least one post-baseline safety measurement. The subjects who answered YES to at least one of the three CIQ questions are in the CIQ "YES" group in the analysis of data in PART B, and subjects who answered NO to all of the CIQ questions are in the CIQ "NO" group.

Descriptive statistics were provided for all of the study data (e.g. mean, standard deviation, frequency, percentage). The Cochran-Mantel-Haenszel test was used to test the primary hypothesis which was, proportion of patients satisfied with once-monthly daily dosing of ibandronate after 6 months of use between the CIQ "YES" and CIQ "NO" groups. The analysis was adjusted with the history of osteoporotic fracture. The Breslow-Day test was used to assess the homogeneity of the odds ratio among the categories of the history of osteoporotic fracture. The absolute change from baseline satisfaction score at month 6, in both composite score and individual domain scores, was calculated. The distribution of the primary end-

Table 1. Demography and osteoporosis history of patients enrolled into Part A of the study

Demography	Patients enrolled into Part A (n=223)
Age (years)	63.7±9.51
Weight (kg)	64.2±10.2
Height (cm)	154.9±6.8
Body mass index (kg/m^2)	26.8±4.3
Time since menopause (months)	210.5±115.1
Osteoporosis history	
Positive history of fractures as an adult	55 (25.5%)
Positive history of osteoporosis-related fragility fracture in a first-degree relative	38 (17.6%)
Current smoker	25 (11.6%)
Time from osteoporosis diagnosis	78.3±50.9 months 6.5±4.2 years

Data are given as n (%) or mean±standard deviation

Table 2. Previous and current diseases, and previous treatments reported in patients enrolled into Part A of the study

Previous or current diseases	Patients enrolled into Part A (n=223)
Any disease	149 (66.8%)
Vascular disorders	93 (41.7%)
Metabolic and nutritional disorders	50 (22.4%)
Musculoskeletal and connective tissue disorders	25 (11.2%)
Cardiac disorder	18 (8.1%)
Endocrine disorders	16 (7.2%)
Gastrointestinal disorders	16 (7.2%)
Psychiatric disorders	15 (6.7%)
Nervous system disorders	10 (4.5%)
Others	40 (17.9%)
Previous treatments	
Previous treatments not associated with osteoporosis	12 (5.4%)
Previous treatments related to osteoporosis	215 (96.4%)
Previous calcium/vitamin D dietary supplement	111 (49.8%)

Data are given as n (%)

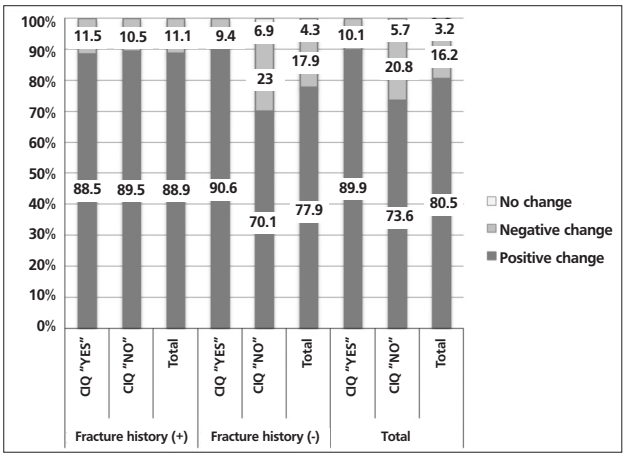

Figure 1. Percentage of subjects with positive, negative or no change in CSS by CIQ-group and history of fractures in ITT population. p=0.0112 in Cochran-Mantel-Haenszel test

Table 3. Laboratory data at baseline and month 6

	Baseline Patients enrolled to Part A (n=223)	Month 6 Safety population (n=192)
White blood cell count (109/L)	6.7±1.8	6.7±1.7
Platelets (109/L)	264.7±64.2	263.0±59.6
Hemoglobin (g/dL)	13.1±1.1	13.1±1.1
Hematocrit (%)	38.9±3.1	39.1±3.1
ALT (U/L)	18.5±8.3	20.0±9.8
Creatinine (mg/dL)	0.77±0.17	0.78±0.17
BUN (mg/dL)	15.4±4.7	15.9±4.8
Albumin (g/dL)	4.4±0.4	4.5±0.4
Sodium (mmol/L)	140.7±9.9	141.5±2.6
Chloride (mmol/L)	104.5±3.2	104.6±3.1
Total calcium (mg/dL)	9.4±0.4	9.5±0.4
Phosphate (mg/dL)	3.6±0.5	3.5±0.5

Data are given as mean±standard deviation

point variable (positive/no change/negative in CSS score) was compared between the CIQ-groups using Pearson chi-square test. The change from baseline satisfaction score and domain scores at month 6 was analyzed using a Wilcoxon test. Mann-Whitney U test was used to compare the domain score changes between the CIQ groups. Statistical significance level was defined as p<0.05.

Results

Study Population

A total of 223 patients (mean age, 63.7±9.51 years) were enrolled in Part A of the study, of which 23 did not continue to Part B (6 patients did not comply selection criteria at entry, 1 patient did not cooperate, 15 patients withdrew consent, and 1 patient had administrative/other problem) enrolling 200 patients to Part B. Four patients enrolled to Part B did not start the study medication, 8 patients were excluded due to major deviation or non-compliance, and 4 patients did not have any safety data, revealing 196 patients for ITT population, 188 patients for per protocol population, and 192 patients for safety population.

The demography and osteoporosis history of patients enrolled into Part A were summarized in Table 1. Among patients enrolled into Part A of the study, 149 (66.8%) had previous or current systemic diseases and 96.4% had previously received treatments related to osteoporosis (Table 2).

The laboratory results at baseline were summarized in Table 3. Serum calcium and phosphate levels were abnormal in 9 (4.0%) and 5 (2.2%) patients, respectively.

CIQ Results

Of the 223 subjects enrolled in Part A of the study and completed the CIQ, 103 (46.2%) patients answered "YES" to one of the questions. Of these patients, 99 (44.4%) would prefer a monthly dosing schedule to their current (daily or weekly) schedule, 25 (11.2%) experienced stomach upset within 48 hours of taking their osteoporosis medication, and 29 (13.0%) missed taking three or more doses of their current (daily or weekly) osteoporosis medication over last 3 months.

OPSAT-Q Results

The OPSAT-Q was completed without assistance by over 98% of the subjects at both visits. The change in the score of each of 16

Table 4. The mean of OPSAT domain scores and change by CIQ total in ITT population

	CIQ "YES" (n=86)				CIQ "NO" (n=110)				
	Baseline	Month 6	Change	*p**	Baseline	Month 6	Change	*p**	*p***
Convenience	68.25±17.56	88.66±9.71	20.11±19.63	<0.0001	75.38±14.86	86.92±9.04	11.45±15.06	<0.0001	0.0005
Quality of life	72.62±17.28	83.24±16.13	10.34±21.04	<0.0001	74.85±18.06	85.06±13.14	10.46±19.95	<0.0001	0.6067
Overall satisfaction	70.44±19.72	85.59±16.23	14.96±25.16	<0.0001	77.58±17.73	87.11±11.90	9.43±20.35	<0.0001	0.0283
Side effects	88.89±17.76	95.94±7.87	7.28±19.28	0.0025	92.88±13.20	93.83±14.20	0.35±18.04	0.6060	0.0487
Total (CSS)	75.05±13.79	89.20±8.59	13.96±15.09	<0.0001	80.17±12.60	88.23±9.82	7.92±14.64	<0.0001	0.0027

Data are given as mean±standard deviation. *Wilcoxon sign rank test for the change from baseline for CIQ groups. **Mann-Whitney U-test for comparison of CIQ "YES" and CIQ "NO" groups

Table 5. The reasons of the dosing preference for 177 patients who prefer the once-monthly dosing schedule

	Intent-to-treat analysis set (n=196)
The once-monthly dosing schedule fits better into my lifestyle	151 (85.3%)
It would be easier to follow the once-monthly dosing schedule for a long period of time	116 (65.5%)
The once-monthly dosing schedule causes less stomach discomfort	78 (44.1%)
It is easier to tolerate side effects overall with the once monthly dosing schedule	74 (41.8%)
I do not agree with any of the above	3 (1.7%)

Data are given as n (%)

Table 6. Summary of adverse events by organ class

	Severity						
	Safety population (n=192)	Mild	Moderate	Severe	Life threatening	Possible/ probable relationship to study drug	Resolved without sequela
Adverse events by any organ class	30 (15.6%)	14 (7.3%)	13 (6.8%)	1 (0.5%)	2 (1.0%)	5 (2.6%)	20 (10.4%)
Gastrointestinal disorders	10 (5.2%)	9 (4.7%)	0	0	1 (0.5%	5 (2.6%)	7 (3.6%)
Infections and infestations	9 (4.7%)	5 (2.6%)	3 (1.6%)	1 (0.5%)	0	0	7 (3.6%)
Musculoskeletal and connective tissue disorders	5 (2.6%)	1 (0.5%)	4 (2.1%)	0	0	0	4 (2.1%)
Injury, poisoning and procedural complications	4 (2.1%)	2 (1.0%)	1 (0.5%)	0	1 (0.5%)	0	3 (1.6%)
Metabolism and nutritional disorders	4 (2.1%)	4 (2.1%)	0	0	0	0	1 (0.5%)
Others	20 (10.4%)	10 (4.05)	3 (1.5%)	0	2 (1.0%)	1 (0.5%)	16 (8.2%)

Data are given as n (%)

Table 7. Concomitant treatments used by safety population

Any concomitant treatment	**350**
HMG CoA reductase inhibitors	26
Salicylic acid and derivatives	26
Beta blocking agents, selective	22
Angiotensin II antagonists and diuretics	14
Selective serotonin reuptake inhibitors	14
Angiotensin II antagonists, plain	13
Dihydropyridine derivatives	13
ACE inhibitors, plain	11
Anilides	10
Others	200
Any concomitant calcium/vitamin D dietary supplement	289
Calcium, combinations with other drugs	133
Vitamin D and analogues	77
Calcium	76
Others	3

Data are given as event number

OPSAT questions was statistically significant in all patients and CIQ "YES" and CIQ "NO" groups except Q14 on heartburn and Q16 on other side effects. The change in the scores of Q11, Q12, Q13, and Q15 was statistically significant for all patients and CIQ "YES" group, but not for CIQ "NO" group. These results were similar in both ITT and PP population.

The mean composite OPSAT domain scores increased between baseline and month 6 for convenience (mean change 15.3±17.7 points), quality of life (mean change 10.4±20.4 points), overall satisfaction (mean change 11.9±22.7 points), and side effects (mean change 3.3±18.8 points). The mean composite OPSAT domain scores at baseline and month 6 for CIQ groups in Table 4. In all domains and total CSS, statistically significant change from baseline was seen except the domain "side effects" in CIQ "NO" group, and there was significant difference between the CIQ groups except for the domain "quality of life".

Number of subjects with positive, negative or no change in total CSS by CIQ groups and history of fractures is presented in Figure 1. There was statistically significant difference between the CIQ groups stratified by fracture status in the proportion of patients with positive change in CSS (P=0.011). The estimated risk ratio was 1.17 (95% CI from 1.03 to 1.32), i.e. the chance of positive change was higher in the CIQ "YES" group.

Preference Questionnaire Results

At month 6, 177 subjects (92.7%) preferred once-monthly dosing schedule, 7 (3.7%) preferred the previous daily/weekly dosing schedule, and 7 (3.7%) did not have preference from one dosing schedule over the other. The reasons of the dosing preference for 177 patients who prefer the once-monthly dosing schedule were summarized in Table 5.

Safety Results

Of the safety population of 192 patients, 30 (15.6%) experienced adverse events. The most frequently reported adverse events were related to gastrointestinal system (10 patients) and infections and infestations (9 patients). Most of the subjects had mild (17 of 30 subjects) or moderate (13 of 30 subjects) adverse events. Two patients had life-threatening adverse events (abdominal pain, postoperative hernia, pulmonary embolism, and acute renal failure). Adverse events in 5 subjects, which were dyspepsia, nausea, and abdominal pain, were evaluated as possibly or probably related to treatment, and 20 subjects with adverse events were resolved without sequela (Table 6).

The most common concomitant treatments used by the safety population were HMG CoA reductase inhibitors (26 subjects), salicylic acid and derivatives (26 subjects), and selective beta blocking agents (22 subjects) (Table 7).

General physical examination findings were normal in over 94% of subjects in both baseline and month 6 assessments. There was no clinically significant difference between baseline and month 6 laboratory values (Table 3).

In the safety population, 190 (99.0%) subjects were compliant (≥80%) with the study treatment.

Discussion

In this prospective and multicenter study, we evaluated the patients' satisfaction, preference and compliance, and tolerability of monthly ibandronate 150 mg in women with postmenopausal osteoporosis who had previously received weekly or daily alendronate or risedronate on the basis of the results of the BONCURE study for Turkish sub-population. We found that patients prefer and are more satisfied and compliant with monthly dosing of ibandronate than daily or weekly bisphosphonate treatment.

To increase compliance of postmenopausal women with long-term bisphosphonates therapy, change of dose regimen is commonly applied (23,24). Furthermore, screening questionnaires can be used to predict patients' satisfaction and to determine those who would benefit from monthly regimen. The CIQ is on of these questionnaires. It includes three questions aimed to identify patients who might prefer or benefit from a monthly regimen rather than a daily or weekly schedule. The questions are on the patient's preference for a monthly schedule, gastrointestinal side effects, and compliance. In our study population, 46.2% patients answered at least one of CIQ questions and defined as CIQ "YES" group. These subjects would prefer monthly regimen (44.4%), experienced gastrointestinal side effects after taking their usual treatment (11.2%), or non-compliant with their current treatment (13.0%). These findings suggest that there is a need for a monthly treatment regimen with bisphosphonates, gastrointestinal side effects are common, and that compliance is an issue for some patients.

Satisfaction with monthly treatment regimen, as determined using the OPSAT-Q, was significantly higher at month 6 compared with baseline in all study population. OPSAT-Q domain scores increased with 6 months of monthly regimen for convenience, quality of life, overall satisfaction, and side effects. Similarly, Bonnick et al. reported that OPSAT-Q composite satisfaction scores improved in 1,678 patients 6 months after switching from weekly oral bisphosphonates to monthly oral ibandronate (19). Statistically significant improvements were recorded for both CIQ "YES" and CIQ "NO" groups for all these domains except the domain "side effects" in CIQ "NO" group. The changes in mean OPSAT-Q scores from baseline to month 6 for the side effects domain in the CIQ "NO" group were not statistically significant for the specific questions about non-gastrointestinal side effects. Additionally, the improvement in OPSAT-Q domain scores was significantly more in the CIQ "YES" group than the "NO" group except for the domain "quality of life". This shows that postmenoposal women who are not compliant with and who had gastrointestinal side effects under weekly or daily regimen, and who initially prefer monthly regimen are more satisfied with monthly bisphosphanate treatment regimen.

The findings of the mean scores for the individual OPSAT-Q questions were supported by the dichotomized CSS scores. Although patients in the CIQ "YES" group were significantly more likely to have a positive change in CSS score compared with patients in the CIQ "NO" group, 70.0% or more patients in both group had positive changes in CSS, irrespective of how they responded to the individual questions in the CIQ.

Most patients (92.7.0%) preferred the monthly dosing schedule. The most common reasons for the preference were that it fitted better into the patients' lifestyles (85.3%) and would be easier to follow for a long period (65.5%). Similar to our findings, Emkey et al. compared monthly ibandronate with weekly alendronate in 342 patients and found that 71.4% preferred monthly ibandronate mostly for the ease of following a treatment regimen for a long time (25).

Almost all of the patients (99.0%) in our safety population were at least 80% compliant with the monthly ibandronate dosing regimen. In the present study, no safety concerns were raised with ibandronate. Only 15.6% of patients experienced adverse events, which were mostly mild or moderate in severity. The most common adverse events were gastrointestinal and infections and infestations (9 patients).

The main limitations of the present study were its open-label design and considerably small sample size. The patients who participate in the study were expecting to prefer the new treatment, which may be considered as a selection bias. However, less than half of the patients (n=99, 44.4%) answered "YES" to the first question of the CIQ which is "Whether the patient would prefer monthly dosing to their current daily or weekly schedule?". The rest of the patients who answered "NO" and would not prefer monthly regimen still participated in the study. In spite of the small sample size, this study provides important regional data on the preference of postmenopausal women with osteoporosis for different dosing regimens of bisphosphonates.

As a conclusion, monthly ibandronate 150 mg treatment has high patients' satisfaction, preference and compliance with good safety profile in women with postmenopausal osteoporosis who had previously received weekly or daily alendronate or risedronate in Turkey.

This study was presented in European Congress on Osteoporosis & Osteoarthritis (ECCEO) Valencia, SPAIN, March 23-26, 2011: "Nurten Eskiyurt and BONCURE Study Group. A Candidate Identification Questionnaire for Patients With Postmenopausal Osteoporosis Switched from Treatment with a Daily or Weekly Bisphosphonate to Once-Monthly Ibandronate—BONCURE: Results of Turkish sub-study. Osteoporos Int 2011; 22 (Suppl 1): 119-408." This study was financially supported by Roche, Turkey.

References

1. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. Lancet 2002;359:1761-7.
2. Delmas PD. Treatment of postmenopausal osteoporosis. Lancet 2002;359:2018-26.
3. Papapoulos SE. Bisphosphonates in the management of postmenopausal osteoporosis. In: Marus R, Osteoporosis, Second Edition, Vol.2: 631-650; 2001.
4. Brown JP, Kendler DL, McClung MR, Emkey RD, Adachi JD, Bolognese MA, et al. The efficacy and tolerability of risedronate once a week for the treatment of postmenopausal osteoporosis. Calcif Tissue Int 2002;71:103-11.
5. Gallagher AM, Rietbrock S, Olson M, van Staa TP. Fracture outcomes related to persistence and compliance with oral bisphosphonates. J Bone Miner Res 2008;23:1569-75.
6. Siris ES, Harris ST, Rosen CJ, Barr CE, Arvesen JN, Abbott TA et al. Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. Mayo Clin Proc 2006;81:1013-22.
7. Huybrechts KF, Ishak KJ, Caro JJ. Assessment of compliance with osteoporosis treatment and its consequences in a managed care population. Bone 2006;38:922-8.
8. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther 2001;23:1296-310.
9. Sclar DA. Improving medication compliance: a review of selected issues. Clin Ther 1991;13:436-40; discussion 5.
10. Reginster JY, Rabenda V. Patient preference in the management of postmenopausal osteoporosis with bisphosphonates. Clin Interv Aging 2006;1:415-23.
11. Richter A, Anton SE, Koch P, Dennett SL. The impact of reducing dose frequency on health outcomes. Clin Ther 2003;25:2307-35; discussion 6.
12. Simon JA, Lewiecki EM, Smith ME, Petruschke RA, Wang L, Palmisano JJ. Patient preference for once-weekly alendronate 70 mg versus once-daily alendronate 10 mg: a multicenter, randomized, open-label, crossover study. Clin Ther 2002;24:1871-86.
13. Payer J, Cierny D, Killinger Z, Sulkova I, Behuliak M, Celec P. Preferences of patients with post-menopausal osteoporosis treated with bisphosphonates–the VIVA II study. J Int Med Res 2009;37:1225-9.
14. Lewiecki EM. Long dosing intervals in the treatment of postmenopausal osteoporosis. Curr Med Res Opin 2007;23:2617-25.
15. Reid DM. Once-monthly dosing: an effective step forward. Bone 2006;38:S18-22.
16. Chesnut IC, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoiseth A, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res 2004;19:1241-9.
17. Reginster JY, Adami S, Lakatos P, Greenwald M, Stepan JJ, Silverman SL, et al. Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2 year results from the MOBILE study. Ann Rheum Dis 2006;65:654-61.
18. Stakkestad JA, Lakatos P, Lorenc R, Sedarati F, Neate C, Reginster JY. Monthly oral ibandronate is effective and well tolerated after 3 years: the MOBILE long-term extension. Clin Rheumatol 2008;27:955-60.
19. Bonnick SL, Silverman S, Tanner SB, Martens M, Bachmann G, Kohles JD, et al. Patient satisfaction in postmenopausal women treated with a weekly bisphosphonate transitioned to once-monthly ibandronate. J Womens Health (Larchmt) 2009;18:935-43.
20. Kastelan D, Lozo P, Stamenkovic D, Miskic B, Vlak T, Kolak Z, et al. Preference for weekly and monthly bisphosphonates among patients with postmenopausal osteoporosis: results from the Croatian PROMO Study. Clin Rheumatol 2009;28:321-6.
21. Hadji P, Minne H, Pfeifer M, Bourgeois P, Fardellone P, Licata A, et al. Treatment preference for monthly oral ibandronate and weekly oral alendronate in women with postmenopausal osteoporosis: A randomized, crossover study (BALTO II). Joint Bone Spine 2008;75:303-10.
22. Flood EM, Beusterien KM, Green H, Shikiar R, Baran RW, Amonkar MM, et al. Psychometric evaluation of the Osteoporosis Patient Treatment Satisfaction Questionnaire (OPSAT-Q), a novel measure to assess satisfaction with bisphosphonate treatment in postmenopausal women. Health Qual Life Outcomes 2006;4:42.
23. de Oliveira Ferreira N, Arthuso M, da Silva R, Pedro AO, Neto AM, Costa-Paiva L. Quality of life in women with postmenopausal osteoporosis: correlation between QUALEFFO 41 and SF-36. Maturitas 2009;62:85-90.
24. Silverman SL, Minshall ME, Shen W, Harper KD, Xie S. Health-Related Quality of Life Subgroup of the Multiple Outcomes of Raloxifene Evaluation Study. The relationship of health-related quality of life to prevalent and incident vertebral fractures in postmenopausal women with osteoporosis: results from the Multiple Outcomes of Raloxifene Evaluation Study. Arthritis Rheum 2001;44:2611-9.
25. Emkey R, Koltun W, Beusterien K, Seidman L, Kivitz A, Devas V, et al. Patient preference for once-monthly ibandronate versus once-weekly alendronate in a randomized, open-label, cross-over trial: the Boniva Alendronate Trial in Osteoporosis (BALTO). Curr Med Res Opin 2005;21:1895-903.