



Evaluation of Patient Satisfaction, Preference and Side Effects after Annual Zoledronic Acid Infusion in Patients with Osteoporosis

Yıllık Zoledronik Asit İnfüzyonu Yapılan Osteoporoz Hastalarında Memnuniyet, Hasta Tercihi ve Yan Etkinin Değerlendirilmesi

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Abstract

Objective: In this study it was aimed to evaluate the patient satisfaction, therapy preference and side-effect profile in patients who receive annual zoledronic acid (ZA) infusion.

Materials and Methods: In this study, 59 patients who had ZA infusion were enrolled. Their demographic and osteoporosis characteristics and the number of received ZA infusions were recorded. A seven-item questionnaire was used to assess the patients' therapy preference. General patient satisfaction, satisfaction during ZA infusion and its effects on life quality were assessed with a Likert scale.

Results: The mean age of the 59 patients (50 females, 9 males) was 68.49±8.65 years. Of the patients 86.4% (51) wanted to continue the same therapy, 64.4% (36) stated that the mode of administration was very convenient and 61% (36) stated that it was well-suited with their lifestyle. The most important factors for the continued usage were the annual administration convenience and the physician's recommendation. Mild side effects (myalgia, arthralgia, flu-like syndrome, fever, headache and pruritus) were reported in 23.7% of the patients (14) subsequent to the first infusion. ZA infusion was quite satisfying for 37.3% of the patients (22) and very satisfying for 40.7% of the patients (24). When the treatment effect on the quality of life was investigated, 42.4% of the patients (25) found it very effective, while 37.3% of them (22) found it extremely effective. Among these patients, 47.5% received their first ZA infusion (28), while 52.5% received multiple (2-4) infusions before (31). The increasing number of infusions did not have any influence on the patient's life quality, satisfaction or therapy preference.

Conclusion: ZA infusion is a preferable, highly satisfactory, convenient therapy and its side effects are well-tolerated, it affects the quality of life favourably.

Keywords: Osteoporosis, zoledronic acid, patient satisfaction, patient preference, adherence, side effect

Öz

Amaç: Bu çalışmada osteoporoz tedavisi için yıllık zoledronik asit (ZA) infüzyonu yapılan hastalarda memnuniyet, hasta tercihi ve yan etki değerlendirilmesinin yapılması amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya ZA infüzyonu yapılmış 59 hasta katıldı. Hastaların demografik ve osteoporoz özellikleri ve ZA infüzyon sayısı sorgulandı. Daha sonra hasta tercihinin sorgulanmasında yedi soruluk bir anket kullanıldı. Hasta genel memnuniyeti, ilacın uygulanması sırasındaki memnuniyet düzeyi, yaşam kalitesi üzerine etkileri Likert skalası ile değerlendirildi.

Bulgular: Çalışmaya alınan 59 (50 kadın, 9 erkek) hastanın yaş ortalaması 68,49±8,65 yıl olarak bulundu. Hastaların %86,4'ü (51) aynı tedaviye devam etmek istediğini, %64,4'ü (36) uygulamanın fazlasıyla kolay olduğunu, %61'i (36) yaşam tarzı ile fazlasıyla uyumlu olduğunu bildirmiştir. İlaça devam ya da kullanımında etkili en önemli faktörlerin yıllık kullanım kolaylığı ve hekimin önerisi olduğu görülmüştür. Hastaların %23,7'sinde (14) ilk infüzyonda hafif yan etkiler (miyalji, artralji, flu like sendrom, ateş, baş ağrısı ve kaşıntı) olduğu bildirilmiştir. ZA infüzyon uygulamasından hastaların %37,3'ünün (22) oldukça, %40,7'sinin (24) fazlasıyla memnun olduğunu bildirmiştir. İlacın yaşam kalitesine etkisi sorgulandığında hastaların %42,4'ü (25) oldukça, %37,3'ü (22) fazlasıyla etkili olduğunu belirtmiştir. Hastaların %47,5'i (28) ilk kez ZA infüzyonu yaptırırken, %52,5'i (31) birden fazla infüzyon (2-4) yaptırmıştı. İnfüzyon sayısındaki artışın yaşam kalitesi, memnuniyet ve hasta tercihini etkilemediği saptanmıştır.

Sonuç: ZA infüzyonu hastalarda tercih edilen, memnuniyet düzeyi yüksek, yaşam kalitesini olumlu etkileyen uygulaması kolay ve yan etkileri tolere edilebilen bir tedavi yöntemidir.

Anahtar kelimeler: Osteoporoz, zoledronik asit, hasta memnuniyeti, hasta tercihi, adherans, yan etki

Introduction

Osteoporosis refers to the structural weakness of the bones, characterised by low bone mass, deterioration of the bone microstructure and the associated high risk of fractures. With the increase in life expectancy, osteoporotic fractures have become an important healthcare problem because of the associated morbidity, mortality and treatment costs (1). Various risk factors, including structural and genetic factors, lifestyle, nutrition, medical conditions and the risk of falls, affect the development of osteoporotic fractures (2). Hormone replacement therapy and bisphosphonates (alendronate, risedronate, ibandronate, zoledronate), raloxifene, teriparatide and denosumab are used for the treatment of osteoporosis. Bisphosphonates have been the first-choice treatment for many years. Various formulations and dosage forms of bisphosphonates are available, including daily, weekly and monthly oral preparations and 3-monthly and annual intravenous (i.v.) forms [zoledronic acid (ZA)]. Oral forms are typically associated with poor gastrointestinal absorption and increased gastrointestinal side effects.

As in other chronic diseases, patient compliance and therapy preference are key considerations in the treatment of osteoporosis. Patient compliance to the treatment of osteoporosis tends to be poorer than that in other chronic conditions (3). The dosing frequency is responsible for the weaker compliance, and less frequent (weekly/monthly) dosage regimes are preferred by the patients. Annual ZA infusion is a treatment option with well-tolerated side effects (headache, flu-like syndrome and bone pain) in patients with osteoporosis (4). It is suggested that patients prefer annual ZA infusions over weekly oral bisphosphonate; however, this subject is not well investigated. A previous study that compared weekly oral alendronate therapy with annual ZA administration showed no difference between the two in terms of the patients' health status and quality-of-life. The study revealed 80.9% patient adherence to weekly oral alendronate therapy. Further, 81% of the patients who received ZA infusions expressed their preference for continuation of the same therapy, while 42.9% of the patients on weekly oral alendronate therapy wanted to shift to annual treatment. The main reasons for the preference of ZA infusion included the challenge of regular drug use, the side effects and the notion of excessive medication (5). In another study, i.v. ibandronate therapy was associated with greater patient satisfaction than weekly treatment with bisphosphonate (6).

The aim of this study was to evaluate the patient satisfaction, patient preference and side-effect profile in patients who receive annual ZA infusions and to evaluate the influence of repeated infusions on these parameters.

Materials and Methods

Data pertaining to 59 patients who received annual ZA infusions in the period between 2010 and 2015 and who were followed up at the outpatient clinic of the Dokuz Eylül

University. The study protocol was reviewed and approved by the Dokuz Eylül University Institutional Review Board (1742 GOA) and informed consent was obtained from all patients. Department of Physical Medicine and Rehabilitation were enrolled in this retrospective study. Patients in the age group of 50-90 years with primary osteoporosis and who were willing to respond to the questionnaire were included, while those with secondary osteoporosis and those reluctant to answer the questionnaire were excluded from the study. The demographic characteristics, age at the diagnosis of osteoporosis, age at the onset of menopause, concomitant diseases, history of low-energy fractures, previous therapies for osteoporosis and the number of the ZA infusions were recorded. Subsequently, patients' preferences were evaluated using a 7-item questionnaire; investigating the willingness to remain on the same therapy or change, ease of medication management, association of medication with lifestyle, convenience to take medication, willingness to continue with the medication and the most important reason for the preference of the drug (5), the prominent reason to continue this medication was also questioned. Medication adherence was defined as a medication possession ratio (MPR), which is a commonly used measure of adherence and is defined as the percentage of days during which the medication was available with the patient during the prescribed duration of treatment. General patient satisfaction, patient satisfaction during the administration of the drug and its effect on pain and the quality of life were evaluated on a Likert scale. The possible drug-related side effects observed within 72 h were also investigated.

Statistical Analysis

All statistical analyses were performed using the SPSS (Statistical Package for the Social Sciences for Windows 16.0) software package. Summary statistics, i.e. the mean, standard deviation, range and frequency (percentage) were calculated. Patients who received the first ZA infusion and those who received multiple ZA infusions were divided into two groups. Intra-group differences with respect to categorical variables were assessed using the McNemar chi-square analysis. The criterion for statistical significance was a p-value of <0.05.

Results

The mean age of the patients was 68.49±8.65 years. The demographic data of the patients are presented in Table 1, and their characteristics related to osteoporosis are summarized in Table 2. Overall, 61% of the patients (n=36) had a chronic

Table 1. Demographic characteristics of patients

Age (mean ± SD) (years)	68.49±8.65
Gender (female/male)	50/9
Education *	33/26
SD: Standard deviation, *Primary school and preprimary school/postprimary school	

disease. Among the patients, 86.4% (n=51) patients stated that they wanted to continue the treatment, 64.4% (n=36) stated that the administration was extremely easy and 61% (n=36) found the therapy very suitable to their lifestyle. The most important factors contributing to treatment adherence or the use of the medication were the annual administration and the physician's recommendation (Table 3). Mild side effects were reported in 23.7% (14) of the patients [myalgia (4), arthralgia (3), flu-like syndrome (3), fever (2), headache (1) and pruritus (1)]. These side effects were only observed after the first infusion. Overall, 37% (22) of the patients were very satisfied and 40.7% (24) were extremely satisfied with the ZA infusion therapy.

With respect to the impact of treatment on the quality of life, 42.4% (25) of the patients found the treatment to be very efficient and 37.3% (22) found it to be extremely efficient (Table 4). Among these patients, 47.5% (28) had received their first ZA infusion, while 52.5% (31) had multiple (2-4) infusions. No relationship was observed between the increase in the number of infusions and the quality of life, patient satisfaction and patient preference (p=0.68, p=0.61 and p>0.05, respectively). The adherence rate at the 2nd, 3rd and 4th infusion was 87.1% (n=22), 82% (n=6) and 92.6% (n=3).

Discussion

Osteoporosis is a chronic disease that requires long-term treatment. It is an important public health problem because of the higher risk of fractures; its social, psychological, economic and physical consequences and its impact on the quality of life. Various treatment options are available for osteoporosis; most require long-term treatment. Patient compliance with treatment is of utmost importance. In this study, patient compliance with ZA infusion was 87.1%, and multiple infusions did not reduce the compliance. Approximately 70% of the patients who received daily administration of bisphosphonate and approximately 60%

of the patients on a weekly dosage regime had discontinued the therapy before the end of the first year. In osteoporotic patients, patient compliance during 1 year of therapy varies between 26% and 70% (3). Failure to comply with the therapy was shown to be associated with an increased risk of fractures (7,8). Dosage interval is one of the key determinants of patient compliance. Cramer et al. (9) and Penning-van Beest et al. (10) reported superior treatment compliance and persistence of treatment with a weekly regime than that with a daily regime. Formulations that incorporate antiresorptive agents to prolong the dosage interval (weekly, monthly and annually)

Table 2. General characteristics associated with osteoporosis

Characteristics	
Menopause age (n=50)	46.48±4.92
Age of osteoporosis diagnosis	55.05±9.80
Body mass index (kg/m ²)	28.75±22.54
History of low energy fracture	28.8% (17)
Previous osteoporosis therapy	
Daily bisphosphonate	16.9% (10)
Weekly bisphosphonate	59.3% (35)
Monthly bisphosphonate	20.3% (12)
i.v. convenient ibandronate	6.8% (4)
Calcitonin	25.4% (15)
Strontium ranelate	16.9% (10)
HRT	1.7% (1)
Numbers of ZA infusion (1) / (2-4)	28/31

i.v.: Intravenous, HRT: Hormon replacement treatment, ZA: Zoledronic acid

Table 3. Therapy preference

Questions	Zoledronic acid (n=59)
Remain on same therapy or change?, n (%)	
Remain on same therapy	51 (86.4%)
Change to alternative treatment	1 (1.7%)
Missing	7 (11.9%)
Easy to manage medication?, n (%)	
Not at all	2 (3.4%)
Somewhat	2 (3.4%)
Very	10 (16.9%)
Extremely	43 (72.9%)
Missing	2 (3.4%)
Medication fits with lifestyle?, n (%)	
Not at all	2 (3.4%)
Somewhat	3 (5.1%)
Very	16 (27.1%)
Extremely	36 (61%)
Missing	2 (3.4%)
Convenient to take medication?, n (%)	
Not at all	2 (3.4%)
Somewhat	5 (8.5%)
Very	9 (15.3%)
Extremely	42 (71.2%)
Missing	1 (1.7%)
Willing to continue to use medication, n (%)	
Not at all	1 (1.7%)
Somewhat	4 (6.8%)
Very	10 (16.9%)
Extremely	38 (64.4%)
Missing	6 (10.2%)
Most important reason for preference, n (%)	
Too many medicines	27 (45.8%)
Not effective	9 (15.3%)
Experienced side effects	14 (23.7%)
Did not like taking pills regularly	12 (20.3%)
Suggest from physiatrist	18 (30.5%)
Intake too inconvenient	16 (27.1%)
Forget other taking pills	6 (10.2%)
Most important reason for continue to use medication, n (%)	
Too many medicines	36 (61%)
Not effective	10 (16.9%)
Experienced side effects	6 (10.2%)
Did not like taking pills regularly	8 (13.6%)
Suggest from physiatrist	3 (5.1%)
Intake too inconvenient	12 (20.3%)
Forget other taking pills	6 (10.2%)

have been shown to be more efficient (11,12). Cotte et al. (13) reported higher 1-year compliance and persistence rates with a monthly dosage regime of ibandronate (85.4%) than those with a weekly administration of bisphosphonate in patients >45 years of age. Schnitzer et al. (14) compared 10 mg of daily alendronate with 70 mg of weekly alendronate and observed that a longer dosing interval is more convenient for patients and enhances treatment compliance in the long run. Cramer et al. (9) reported compliance rates of 40% and 55% in patients on daily and weekly regimes of bisphosphonate administration, respectively. In a study by Solomon et al. (15), 1-year adherence to osteoporosis treatment was 36%; the variables associated with lower adherence were a history of failure to comply with long-term therapies, concerns about side effects, concurrent treatment with multiple drugs, underestimation of the seriousness of osteoporosis as a condition/disease, disregard for the potential of an osteoporotic fracture to result in disability, distrust in the therapy may help the patient to stay active and frequent use of alcohol.

Although oral bisphosphonate have confirmed the efficacy in reducing fragility fractures, poor adherence limits their clinical utility and negatively impacts the outcomes. Data from two US claims databases showed that treatment adherence (MPR >80%) reduced nonvertebral fracture risk by 20% and that of hip fracture risk by 45% ($p < 0.001$ for both). Although adherence levels <50% did not affect the risk of fractures, the risk decreased as adherence increased above 50%, and a steep improvement was observed at an adherence level between 75% and 100%. The abovementioned UK study showed no reduction in the risk of fractures in patients who received <6 months of therapy. These data point to maximal benefit with maximum adherence. They also suggest that even with some degree of drug use, suboptimal adherence can lead to a total loss of any benefit (16). In our study, our compliance may help to reduce the risk of fracture.

The side effects of ZA infusion are generally well characterized. The most commonly reported adverse events were post-dose symptoms such as pyrexia, myalgia, headache, arthralgia or flu-like syndrome. Any or a combination of these primarily occurred following the first infusion (31.6%). These progressively decreased with subsequent infusions; only 2.8% experienced these symptoms after the third infusion (16). In our study, the frequency of side effects diminished with repeated infusions. In a previous study, ZA and denosumab were compared in terms of efficiency, side effects and patient satisfaction; both drugs were associated with comparable efficiency and patient satisfaction. In terms of side effects, mild flu-like syndrome was observed significantly more frequently with ZA. In our study, patient satisfaction was rather high after ZA infusion. Side effects, including myalgia, arthralgia and mild flu-like syndrome, were also observed more frequently; however, serious side effects such as sympathomimetic arrhythmia were not observed. Still, no electrocardiograms were taken from the patients. In particular, paracetamol/non-steroid anti-inflammatory drugs taken prior to the infusion may have relieved the mild side effects (17). Conversely, in a study that investigated ZA infusions administered to 259 elderly patients, approximately one-third of the patients refused to accept a second infusion. The related factors were observed to be female gender, post-infusion syndrome and the route of administration. It has been suggested that these patients should be given information by the physician. In our study, the most important factors that influenced the preference for the once-yearly ZA infusion were annual administration and recommendation by the physician; 86% patients wanted to continue this therapy modality. This result underlines the importance of patient education on the treatment and side effects (18).

Osteoporosis may affect the patients' quality of life because of pain, reduced back muscle strength, loss of flexibility, vertebral deformities, mood changes and vertebral or non-vertebral fractures (19). In patients with osteoporosis, the quality of life is an important criterion for determining treatment strategy and assessing therapeutic efficacy. Dosing interval is a key determinant of patient compliance; drug regimens with longer dosing intervals tend to elicit better patient compliance, which in turn improves the quality of life (20). We did not evaluate the quality of life with a separate scale in our study. However, we have investigated the impact of ZA on the quality of life through a Likert-type of scale; majority of the patients found it to be efficient in this respect.

The small sample size and the retrospective study design are the key limitations of our study.

Table 4. The effect of zoledronic acid in patient satisfaction, pain and quality of life

Patient satisfaction	
Not at all	1 (1.7%)
Somewhat	6 (10.2%)
Very	22 (37.3%)
Quite	6 (10.2%)
Extremely	24 (40.7%)
Pain	
Not at all	26 (44.1%)
Somewhat	13 (22%)
Very	5 (8.5%)
Quite	7 (11.9%)
Extremely	8 (13.6%)
Quality of life	
Not at all	3 (5.1%)
Somewhat	1 (1.7%)
Very	25 (42.4%)
Quite	8 (13.6%)
Extremely	22 (37.3%)

Conclusion

In conclusion, based on the results of our study, annual ZA infusion for the treatment of primary osteoporosis seems to be a convenient and well-tolerated therapeutic modality, which is

associated with good patient compliance, patient satisfaction and a positive impact on the quality of life.

Ethics

Ethics Committee Approval: The study protocol was reviewed and approved by the Dokuz Eylül University Institutional Review Board (1742 GOA, 2014/33-06 decision number, 30.10.2014),
Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.D., S.G., Design: B.D., D.E., Data Collection or Processing: E.Ş., D.E., D.B., Analysis or Interpretation: S.G., B.D., Literature Search: E.Ş., B.D., Writing: B.D., S.G.

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References

1. Sinaki M. Prevention and treatment of osteoporosis, In: Braddom RL (ed). Physical Medicine and Rehabilitation. 5th edition, Elsevier, USA 2007;pp.3-9.
2. Torgerson DJ, Campbell MK, Reid DM. Life style, environmental and medical factors influencing peak bone mass and bone loss in postmenopausal osteoporosis; 12 years study. *Br J Rheumatol* 1995;34:620-4.
3. Cramer JA, Gold DY, Silverman SL, Lewiecki EM. A systematic review of persistence and compliance with bisphosphonates for osteoporosis. *Osteoporos Int* 2007;18:1023-31.
4. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356:1809-22.
5. Hadji P, Ziller V, Gamerding D, Spieler W, Articus K, Baier M, et al. Quality of life and health status with zoledronic acid and generic alendronate- a secondary analysis of the Rapid Onset and Sustained Efficacy (ROSE) study in postmenopausal women with low bone mass. *Osteoporosis int* 2012;23:2043-51.
6. Hadji P, Mine 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.
7. Caro JJ, Ishak KJ, Huybrechts KF, Raggio G, Naujoks C. The impact of compliance with osteoporosis therapy on fracture rates in actual practice. *Osteoporos Int* 2004;15:1003-8.
8. 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.
9. Cramer JA, Amonkar MM, Hebborn A, Altman R. Compliance and persistence with bisphosphonate dosing regimens among women with postmenopausal osteoporosis. *Curr Med Res Opin* 2005;21:1453-60.
10. Penning-van Beest FJ, Goettsch GW, Erkens JA, Herings RM. Determinants of persistence with bisphosphonates; a study in women with postmenopausal osteoporosis. *Clin Ther* 2006;28:236-42.
11. Sambrook P. Compliance with treatment in osteoporosis patients an ongoing problem. *Aust Fam Physician* 2006;35:135-7.
12. Boonen S, Rizzoli R, Meunier PJ, Stone M, Nuki G, Syversen U, et al. The need for clinical guidance in the use of calcium and vitamin D in the management of osteoporosis; a consensus report. *Osteoporos Int* 2004;15:511-9.
13. Cotte FE, Fardellone P, Mercier F, Gaudin AF, Roux C. Adherence to monthly and weekly oral bisphosphonates in women with osteoporosis. *Osteoporos Int* 2010;21:145-55.
14. Schnitzer T, Bone HG, Crepaldi G, Adami S, McClung M, Kiel D, et al. Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. Alendronate Once-Weekly Study Group. *Aging (Milano)* 2000;12:1-12.
15. Solomon DH, Brookhart MA, Tsao P, Sundaresan D, Andrade SE, Mazer K, et al. Predictors of very low adherence with medications for osteoporosis; towards development of a clinical prediction rule. *Osteoporos Int* 2011;22:1737-43.
16. Carmona R, Adachi R. Treatment of postmenopausal osteoporosis patient perspectives focus on once yearly zoledronic acid. *Patient Preference and Adherence* 2009;3:189-93.
17. Sheedy KC, Camara MI, Camacho PM. Comparison of the efficacy, adverse effects, and cost of zoledronic acid and denosumab in the treatment of osteoporosis. *Endocr Pract* 2015;21:275-9.
18. Lee YK, Nho JH, Ha YC, Koo KH. Persistence with intravenous zoledronate in elderly patients with osteoporosis. *Osteoporos Int* 2012;23:2329-33.
19. Lips P, Van Schoor NM. Quality of life in patients with osteoporosis. *Osteoporosis Int* 2005;16:447-55. (PMID:15609073).
20. Madenci E, İbas E, Koca İ, Altındağ Ö. Effect of Patient Follow-Up System on the Treatment Compliance of Osteoporotic Patients and on Quality of Life. *Turkish Journal of Osteoporosis* 2014;20:46-50.