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Prevalence of Non-Responders to Both Oral Bisphosphonate Monotherapy and Intravenous Ibandronate in Patients with Postmenopausal Osteoporosis

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Abstract

Objectives: Although bisphosphonates (BPs) are effective for the majority of patients with osteoporosis, some individuals do not adequately respond to these drugs. The objective of this study was to estimate the prevalence of true BP non-responders who showed insufficient response after both oral BPs and intravenous ibandronate. **Methods:** Among 146 consecutive patients with postmenopausal osteoporosis who received oral BP monotherapy for more than 12 months, insufficient responders to oral BP monotherapy were switched to intravenous ibandronate injection and followed for more than 12 months. Serum N-terminal telopeptide of type I collagen (NTX) and bone alkaline phosphatase (BAP) concentrations were measured. Patients who also showed insufficient response to intravenous ibandronate were defined as true BP non-responders. Insufficient response to BP therapy was evaluated based on the serum NTX reduction cut-off for minimum significant change. **Results:** Sixty-one patients (41.8%) were diagnosed as oral BP non-responders. Fourteen patients who switched to intravenous ibandronate and had complete data available were used for final analysis. After switching to intravenous ibandronate, both NTX and BAP decreased significantly ($p < 0.05$). However, at 6 - 12 months after switching, 57.1% - 64.3% of patients still showed insufficient response of NTX as compared to baseline (before oral BP monotherapy), and 21.4% - 35.7% of patients still showed insufficient response of NTX when compared to data immediately before switching. **Conclusion:** These results estimated that as few as 9% - 15% (*i.e.*, 21.4% - 35.7% of 41.8%) or as many as 24% - 27% (*i.e.*, 57.1% - 64.3% of 41.8%) of patents might be true BP non-responders.

Keywords

Bone Resorption, Biphosphonates, Ibandronic Acid, Osteoporosis, Prevalence

1. Introduction

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing a person to increased risk of fracture [1]. Fracture risk in osteoporosis increases with age, particularly among women. The overall 10-year fracture risk at 50 years old is reportedly 9.8% in women and 7.1% in men, compared to 21.7% in women and 8% in men at 80 years old [2]. Anti-osteoporotic pharmacotherapy is the most important and essential option for preventing osteoporotic fractures. Among multiple therapeutic options available for pharmacotherapy against osteoporosis, bisphosphonates (BPs) are the first-line drugs and act strongly to reduce osteoclast-mediated bone resorption [3].

BPs can be administered either orally or intravenously, but are commonly used as oral medication. However, the prevalence of an inadequate response to oral BPs varies widely among different studies, varying from 8% to 60% [4]-[11]. Although the wide variety in methods of evaluation, including poor response in bone turnover markers, ineffectiveness in changing bone mineral density (BMD), or incident osteoporotic fractures, would have contributed to the wide range in prevalence, the evidence suggests that non-responders to oral BPs actually exist.

Treatment non-response to oral BPs could have a number of causes, including non-compliance, non-persistence, some underlying, untreated cause of osteoporosis, an inability to absorb the drug [12], or insufficiency of vitamin D [5] [7] [9] [13]. Upper gastrointestinal adverse events have been reported with oral BPs and are a strong predictor of non-adherence [14]. Studies have shown that maintenance vitamin D status is required for optimal therapeutic efficacy of BPs [5] [15]. However, the most important probable cause of non-response is an extremely low bioavailability via the oral route [3] [16]. Many BPs have a gastrointestinal absorption rate below 1% [3] [16], and this low value may be further reduced by the specific conditions of the individual patient.

Administration of BPs via an intravenous route is thus theoretically preferable. However, studies have reported that intravenous BPs also have non-responders [4] [5]. The most suspected cause of inadequate response to intravenous BP treatment is vitamin D insufficiency, but the details remain unclear. Bae *et al.* [4] investigated the effect of intravenous administration of ibandronate in 13 patients with osteoporosis who had shown insufficient response to orally administered BPs. After intravenous ibandronate administration, serum levels of C-terminal telopeptide of type I collagen (CTX), a bone resorption marker, were significantly reduced [4]. However, in that study, because all subjects received supple-

ments of more than 800 IU of vitamin D, pure effects of BPs remain unclear, and the number or rate of non-responders after intravenous ibandronate has not been reported.

In clinical settings, many doctors prescribe a single drug for treatment, and monotherapy is also often preferred over polypharmacy by the medical insurance system. However, no studies appear to have reported the true prevalence of treatment failure (*i.e.*, except for the combined effects of vitamin D) after BP monotherapy. This study first investigated the prevalence of non-responders to oral BP monotherapy among patients with postmenopausal osteoporosis using serum N-terminal telopeptide of type I collagen (NTX) as a marker. Second, we tested the effects of intravenous ibandronate among patients with insufficient changes to NTX after oral BP monotherapy to identify "true" non-responders to BPs.

2. Patients and Methods

2.1. Subjects

A total of 146 consecutive female patients with postmenopausal osteoporosis ≥ 50 years old who received oral BP monotherapy (alendronate, risedronate, or minodronate) at our outpatient clinic for more than 12 months (41 ± 20 months; range, 12-78 months), who demonstrated ≥ 80% compliance over the treatment period, and who had data available on bone turnover markers at both baseline and follow-up were enrolled. Osteoporosis was diagnosed according to the criteria proposed by the Japanese Society for Bone and Mineral Research (2012 revision) [17]. Briefly, patients with: 1) fragility fracture in either the lumbar spine or proximal femur; 2) other fragility fracture and BMD < 80% of the young adult mean (YAM); or 3) BMD ≤ 70% or 2.5 standard deviations (SDs) below the YAM were diagnosed as having osteoporosis. All administered doses of oral alendronate (35 mg/week), risedronate (17.5 mg/week), or minodronate (50 mg/month) were the licensed doses in Japan.

In this study, patients receiving combination therapy with any other antiosteoporosis agents (vitamin D, menatetrenone, teriparatide, etc.) were excluded. To investigate definitive effects of oral BP, patients with upper gastrointestinal diseases such as reflux esophagitis or delayed esophageal emptying or active gastric/duodenal ulcer and who were unable to maintain an upright position for at least 60 min were excluded.Because bone turnover markers were influenced by metabolic bone diseases and fresh fractures, we also excluded patients with: 1) a history of metabolic bone disease other than primary osteoporosis; 2) malignancy; 3) secondary osteoporosis including diabetes mellitus and glucocorticoid usage; 4) current smoking; 5) any documented fracture within the preceding 1 year prior to starting oral BP therapy; or 6) any fracture after oral BP therapy.

A total of 146 patients with BP monotherapy were divided into oral BP responders and non-responders due to changes in serum NTX levels from baseline.

All oral BP non-responders were then recommended to switch to intravenous administration of ibandronate (1 mg/month). The decision on whether to switch to intravenous ibandronate was made by each patient. Patients who agreed to switch intravenous ibandronate were followed-up for more than 12 months and bone turnover markers at 6 and 12 months after switching to intravenous ibandronate were evaluated.

All participants provided informed consent. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study protocol was approved by the ethics committee of the Akita University Graduate School of Medicine (IRB #1970).

2.2. Measurement of Bone Turnover Markers

Blood was collected before and after treatment in all patients. Serum levels of NTX as a marker for bone resorption and bone-specific alkaline phosphatase (BAP) as a marker for bone formation were measured before and after oral BP treatment. Furthermore, in patients who switched to intravenous ibandronate, NTX and BAP were also measured at 6 and 12 months after switching to intravenous ibandronate. NTX was measured by enzyme-linked immunosorbent assay (Osteomark; Mochida Pharmaceutical, Tokyo, Japan; reference range, 10.7 - 24.0 nmol bone collagen equivalent (BCE)/L), and BAP was measured by chemiluminescent enzyme immunoassay (Access Ostase; Beckman Coulter, Tokyo, Japan; reference range, 3.8 - 22.6 μg/L). Intra-assay coefficient of variation (CV) of serum NTX and BAP were 6.9% and 3.2%, respectively. Inter-assay CV of serum NTX and BAP were 15.5% and 10.2%, respectively [18].

In this study, reduction of NTX exceeding the minimum significant change (MSC) was used as the criterion for evaluating BP treatment effectiveness. MSC is defined as twice the inter-day variation in the morning in premenopausal women [19]. MSC has been reported as 16.3% for serum NTX, and 9.0% for serum BAP [19]. If the serum NTX level in patients receiving BP therapy showed insufficient changes and did not decrease more than the MSC from baseline, the patient was defined as a BP non-responder.

2.3. Statistical Analyses

Results are expressed as median [lower and upper quartile]. Based on the Bartlett test, data did not show normal distributions. Time-dependent changes in NTX, BAP, and percentage changes in these parameters were assessed using a Friedman test, followed by the Bonferroni method for multiple comparisons. The differences between the time points of 6 and 12 months after ibandronate treatment were analyzed using a Wilcoxon rank-sum test. Differences with a value of $p < 0.05$ were considered statistically significant. All statistical analyses were performed using EZR [20].

3. Results

3.1. Rate of Non-Response to Oral Administration of BPs and Patients Who Switched to Intravenous Ibandronate

A flow chart of patient disposition is shown in Figure 1. Among the 146 patients who received oral BP monotherapy for more than 12 months, 61 patients (41.8%) were diagnosed as non-responders based on an insufficient reduction in serum NTX compared to the cut-off of the MSC.

All 61 non-responders to oral BP monotherapy were recommended to switch to intravenous ibandronate treatment, since the intravenous administration could be expected to provide more definitive effectiveness by excluding concerns regarding gastrointestinal absorption. Among these non-responders, 22 patients (36.1%) agreed to switch. All the remaining 39 patients who declined to switch gave a dislike of injections as the reason for declining.

The 22 patients who switched were treated with intravenous ibandronate for more than 12 months. Concentrations of bone turnover markers (NTX and BAP) were evaluated at 6 and 12 months after switching to ibandronate. However, 8 patients were excluded from the final analysis because of missing data for bone turnover markers. The final sample thus comprised the 14 patients who completed the study, with a mean age of 74.7 ± 5.5 years. Before and after oral BP monotherapy, Serum NTX levels showed a significant increase from before BP monotherapy (14.0 nmolBCE/L [13.3, 19.1 nmolBCE/L]) to after BP monotherapy (18.0 nmolBCE/L [15.5, 19.7 nmolBCE/L]; p = 0.0312). Among these, 5 patients initially received oral alendronate, 6 received risedronate, and 3 received minodronate, with no significant difference in distributions of age and concentration of bone turnover markers between the three drugs (data not shown).

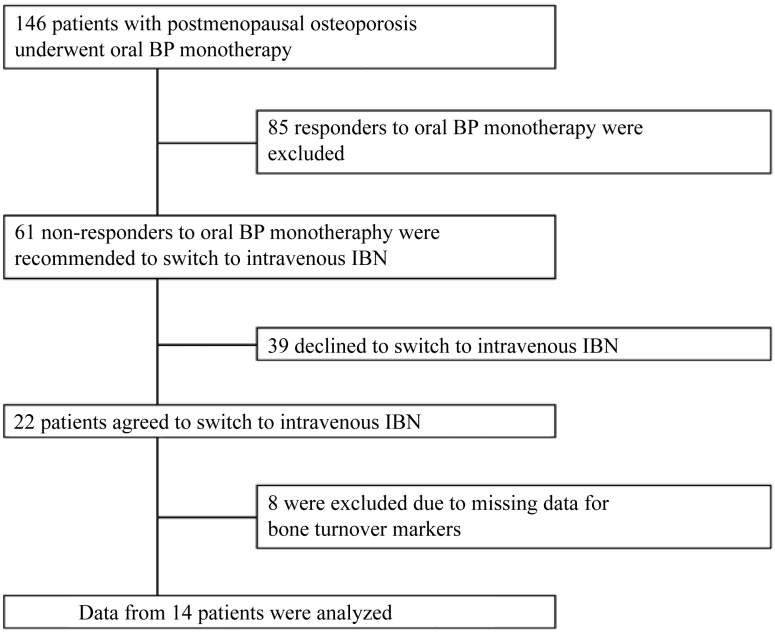

Figure 1. Flow chart of patient disposition. BP, bisphosphonate; IBN, ibandronate.

3.2. Efficacy of Intravenous Administration of Ibandronate in Oral BP Non-Responders

Changes in bone turnover markers among the 14 oral BP non-responders who switched to intravenous ibandronate are shown in Table 1. Both serum NTX and BAP concentrations changed significantly ($p < 0.0001$ and $p = 0.0003$, respectively) throughout the study. Compared to baseline (before oral BP monotherapy), percent changes in NTX and BAP were significant after switching to ibandronate.

We further counted the number of patients for whom changes in bone turnover markers were less than the MSC even after switching to intravenous administration of ibandronate (Table 2). Patients for whom the reduction in NTX did not reach below the MSC after switching to intravenous ibandronate were treated as true BP non-responders. Compared to baseline, the number of true BP non-responders was 9 (64.3%) at 6 months and 8 (57.1%) at 12 months after switching to intravenous ibandronate. Compared to the time just before switching to intravenous ibandronate, the number of true non-responders was 3 (21.4%) at 6 months and 5 (35.7%) at 12 months. Similar trends were seen in the number of patients with BAP changes to less than the MSC.

4. Discussion

4.1. Rate of True BP Non-Responders as Estimated by the MSC of Serum NTX

This study attempted to elucidate the prevalence of true BP non-responders. First, this study revealed the prevalence of non-responders to oral BP monotherapy in postmenopausal osteoporosis using serum NTX as a marker was 41.8%, even though the enrolled patients demonstrated ≥ 80% compliance and did not have secondary osteoporosis. A compliance rate of 70% - 80% is widely accepted

Table 1. Changes of bone turnover markers before and after switching to intravenous IBN in oral BP non-responders (n = 14).

	Before switching to IBN		After switching to IBN		Friedman/ Wilcoxon#
	Before oral BP (T1)	After oral BP (T2)	6 months (T3)	12 months	
Serum NTX (nmolBCE/L)	14.0 [13.3, 19.1]	18.0 [15.5, 19.7]*	13.3 [12.0, 15.9]**	12.9 [11.0, 15.7]***	< 0.0001
% change vs. T1		21.7 [3.0, 32.1]	-3.8 [-21.8, -0.2]***	-10.3 [-23.6, -1.3]***	0.0003
% change vs. T2			-27.3 [-32.5, -17.7]	-25.8 [-38.0, -9.0]	0.5760#
% change vs. T3				-0.9 [-9.2, 1.9]	
Serum BAP (μg/L)	10.3 [8.4, 11.5]	10.5 [9.5, 11.3]	9.1 [7.7, 9.8]*,**	9.5 [8.1, 10.9]	0.0003
% change vs. T1		5.5 [-4.5, 17.3]	-10.5 [-18.8, -4.4]***	-8.6 [-14.5, 0.7]	0.0003
% change vs. T2			-17.1 [-22.2, -14.8]	-14.2 [-19.3, -10.5]	0.0303#
% change vs. T3				4.1 [0.8, 7.8]	

Median [lower, upper quartile]; IBN, ibandronate; BP, bisphosphonates; NTX, serum N-terminal telopeptide of type I collagen; BAP, bone-specific alkaline phosphatase; T1, beginning of study (baseline); T2, after treatment with oral BP; T3, 6 months after treatment with IBN. *$p < 0.05$ vs. T1 by Bonferroni method; **$p < 0.05$; ***$p < 0.01$ vs. T2 by Bonferroni method.

Table 2. Number and percentage of patients showing changes in bone turnover markers less than MSC (n = 14).

	Before switching to IBN	After switching to IBN	
	After oral BP (T2)	6 months	12 months
Number with less than MSC (16.3%) in serum NTX			
vs. T1 (%)	14 (100%)	9 (64.3%)	8 (57.1%)
vs. T2 (%)		3 (21.4%)	5 (35.7%)
Number with less than MSC (9.0%) in serum BAP			
vs. T1 (%)	11 (78.6%)	7 (50.0%)	7 (50.0%)
vs. T2 (%)		3 (21.4%)	3 (21.4%)

IBN, ibandronate; BP, bisphosphonates; MSC, minimum significant change; NTX, serum N-terminal telopeptide of type I collagen; BAP, bone-specific alkaline phosphatase; T1, beginning of study (baseline); T2, after treatment with oral BP.

as necessary to obtain effective pharmacotherapy against osteoporosis [21]. Secondary osteoporosis is a possible additional factor associated with inadequate response to BP therapy [6] [8] [10] [15] [22] [23].

Second, this study demonstrated the existence of true BP non-responders who responded to neither oral nor intravenous BPs. Treatment with BPs given intravenously might be a reasonable option in patients who fail to respond to orally administered BP due to malabsorption. In this study, serum NTX significantly decreased after switching to intravenous ibandronate in patients with insufficient changes in serum NTX after oral BP monotherapy. Serum BAP also showed similar changes after starting intravenous ibandronate, indicating that bone turnover decreased after this switch. However, the present study showed that the change in serum NTX in some patients did not reach the MSC. Our results showed that compared to the time point just before switching to intravenous ibandronate, the rate of non-responders to intravenous ibandronate was 21.4% at 6 months and 35.7% at 12 months. Compared to baseline (before oral BP therapy), the rate of non-responders to intravenous ibandronate was 64.3% at 6 months and 57.1% at 12 months. According to these results, the estimated prevalence of true BP non-responders among patients with postmenopausal osteoporosis might be as low as 9% - 15% (*i.e.*, 21.4% - 35.7% of 41.8%) or as high as 24% - 27% (*i.e.*, 57.1% - 64.3% of 41.8%).

This study used bone turnover markers to identify response to BP treatment, because serial concentrations of bone turnover markers may prove more useful than serial BMD for early identification of response to pharmacotherapy. The ability to identify non-responders as early as possible can be beneficial, allowing changes in management strategy. Repeated BMD measurement is commonly used to monitor treatment response, but shows limitations in that changes due to treatment can take longer to become detectable [12], and the National Osteoporosis Foundation recommends a 2-year interval after treatment [24]. However,

the findings obtained in this study should be reconfirmed with BMD measurements in future investigations.

4.2. Probable Causes of BP Non-Response

Published studies have demonstrated that, in addition to a lack of adequate compliance to the treatment and secondary osteoporosis, vitamin D insufficiency and reduced calcium intake can also be confounding conditions for ineffectiveness of BP therapy [4]-[11] [15] [22]. Peris *et al*. [9] suggested that maintenance of 25(OH)D levels at > 30 ng/ml is indicated for adequate response to BP treatment.

The present study used ibandronate as an intravenously administrational BP. Ibandronate is a potent BP for the treatment of osteoporosis and can be used orally or intravenously [25]. However, one study reported that the rate of non-response to intravenous ibandronate (1 mg/month), as evaluated by BMD and urinary CTX from baseline to 1 year, was 6.1% [26]. That study also showed that mean 25(OH)D levels were significantly lower among non-responders than among responders [26]. Thus, 25(OH)D level appears important as an indicator of treatment response with intravenous ibandronate.

In contrast, Cairoli *et al*. [23] reported that among 97 postmenopausal women with primary osteoporosis, 25.8% responded inadequately to BPs (alendronate or risedronate), despite good compliance to therapy and normal 25(OH)D levels [23]. In that study, treatment failure was defined by incident fragility fractures and/or decreased BMD. In addition, Bourke *et al*. [27] suggested with the results from a larger population study that dietary calcium intake and baseline vitamin D status had no influence on the effects of zoledronate at 1 year. Reasons for the ineffectiveness of BP independent of vitamin D status remain unclear, but a study by Cairoli *et al*. [23] concluded that current smoking and bone turnover in the upper part of the normal range were associated with inadequate response to BPs [23]. Moreover, more recent studies have shown that genetic polymorphisms in the genes involved in the main pathways for the mechanisms of BP action influence response to BP therapy [28]. In the present study, no patients were current smokers, but vitamin D status could not be evaluated because 25(OH)D measurements were not covered by the national insurance system in Japan when we performed this study.

4.3. Limitations

This study showed strength in estimating the prevalence of true BP non-responders by evaluating serial treatment after oral and intravenous BPs. The study was not randomized, but was conducted in a prospective manner. Our data were obtained from "real-life" practice. However, limitations to this study should also be noted. Because this study attempted to elucidate the effects of BP monotherapy, patients receiving co-therapy with vitamin D were excluded. In clinical settings, drug monotherapy is sometimes preferable according to the medical insurance system. However, our study design lacked information concerning potential con-

founders such as 25(OH)D status, or supplements and/or dietary intake of vitamin D. Various forms of oral BPs (alendronate, risedronate, or minodronate) were administered prior to the ibandronate treatment. The various forms of oral BPs may cause a different change of bone turnover markers after switching to the ibandronate. In addition, the number of subjects included in the final analysis was small. Further studies with a larger number of subjects and evaluation of 25(OH)D status are anticipated to reconfirm the findings obtained from this study.

5. Conclusion

Among 146 patients with postmenopausal osteoporosis who received oral BP monotherapy, 41.8% were diagnosed as oral BP non-responders based on a serum NTX reduction below the MSC. Among oral BP non-responders, rates of non-responders to intravenous ibandronate at 6 - 12 months after administration were 57.1% - 64.3% and 21.4% - 35.7% when compared to data from baseline or just before switching to ibandronate, respectively. Based on these results, the prevalence of true BP non-responders in postmenopausal osteoporosis was estimated to be as low as 9% - 15% or as high as 24% - 27%.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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