Rationale, baseline characteristics and methodology of the non-interventional VIVA* study in postmenopausal osteoporosis

P. Hadji[1]; L. C. Hofbauer[2]; D. Felsenberg[3]; M. Amling[4]; A. Kurth[5]

[1]Philipps University of Marburg, Department of Gynaecology, Reproductive Medicine and Osteoporosis, Marburg, Germany; [2]Division of Endocrinology, Diabetes and Bone Metabolic Disorders, University Medical Center, Technical University Dresden, Dresden, Germany; [3]Charité University Medicine Berlin, Campus Benjamin Franklin, Center for Muscle and Bone Research, Berlin, Germany; [4]University Hospital Hamburg-Eppendorf, Hamburg, Germany; [5]Specialty hospital Ratingen, Centre for Orthopaedics and Rheumatology, Ratingen, Germany

Keywords
Osteoporosis, fracture, compliance, ibandronate, alendronate

Summary

Background: It is important to understand compliance and persistence with medication use in the clinical practice of osteoporosis treatment. The purpose of this work is to describe the "intravenous ibandronate versus oral alendronate" (VIVA) study, a non-interventional trial to assess the compliance and persistence of osteopenic post-menopausal women with treatment via weekly oral alendronate or intravenous ibandronate (Bonviva®) every three months.

Methods: 4477 patients receiving ibandronate 3 mg i. v. quarterly and 1491 patients receiving alendronate 70 mg orally weekly were included in the study. Matched pairs of 901 subjects in each group were also generated. Matching was performed on the basis of age, body mass index, fracture history at study inclusion, prior treatment with bisphosphonates and the number of concomitant disorders. Secondary outcome measures of osteoporosis related fractures, mobility restriction and pain, analgesia, quality of life questionnaires as well as attitudes to medications were assessed. The primary outcome parameters of compliance and persistence will be tracked in these subjects.

Results: At baseline, the entire collectives differed significantly on body weight (less in ibandronate group), duration since osteoporosis diagnosis (longer in ibandronate), and incidence of prior osteoporotic fracture (higher in ibandronate group). The matched-pairs differed only on mobility restriction and quality of life (both worse in ibandronate group).

Conclusion: The results from the VIVA study trial will provide scientific rationale for clinical recommendations in the pharmacological treatment of postmenopausal osteoporosis.

Correspondence to
Prof. Dr. med. Peyman Hadji
Department of Gynaecological Endocrinology, Reproductive Medicine, and Osteoporosis
Philipps-University of Marburg
Baldingerstrasse, 35033 Marburg, Germany
Tel.: +49 (0) 64 21/586-64 86
Fax: +49 (0) 6421/586-70 70
E-Mail: hadji@med.uni-marburg.de

Rationale, Ausgangscharakteristika sowie Methodologie der nichtinterventionellen Studie VIVA bei postmenopausalen Frauen mit Osteoporose
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* VIVA = intravenous ibandronate versus oral alendronate

Schlüsselwörter
Osteoporose, Fraktur, Therapietreue, Ibandronat, Alendronat

Zusammenfassung

Hintergrund: Es ist von großer Wichtigkeit, die Faktoren zu identifizieren, welche die Therapietreue in der Behandlung der postmenopausalen Osteoporose maßgeblich beeinflussen. Zielsetzung der vorliegenden VIVA-Studie, einer nichtinterventionellen Untersuchung, war es, die Therapietreue (Compliance und Persistenz) bei postmenopausalen Frauen mit Osteoporose, die auf eine einmal wöchentliche, orale Alendronat-Therapie oder eine i. v.-Ibandronat-Therapie gesetzt wurden, zu untersuchen.

Methoden: 4477 Patienten, die Ibandronat 3 mg i. v. einmal im Quartal erhielten, und 1491 Patienten, die Alendronat 70 mg einmal pro Woche erhielten, wurden in die Studie eingeschlossen. Zusätzlich erfolgte eine Matched-Pair-Analyse von jeweils 901 Patientinnen aus beiden Gruppen. Das Matching erfolgte auf der Basis von Alter, Body-Mass-Index, prävalenten Frakturen bei Studieneinschluss, vorheriger Behandlung mit Bisphosphonaten sowie der Anzahl von Begleitmedikationen. Zu den sekundären Endpunkten zählten prävalente osteoporoseassoziierte Frakturen, Mobilität und Schmerzen, Analgetikaverbrauch, Lebensqualität sowie die Einstellung zur Medikation. Alle o. g. Faktoren werden im Rahmen der VIVA-Studien untersucht.

Ergebnis: Bei Studieneinschluss zeigte sich ein signifikanter Unterschied zwischen beiden Untersuchungsgruppen in Bezug auf das Körpergewicht, den Zeitpunkt der Osteoporosediagnose und der Inzidenz prävalenter osteoporotischer Frakturen. Nach Einsetzen des Matched-Pair-Verfahrens zeigten sich nur noch Unterschiede in der Mobilität und der Lebensqualität.

Schlussfolgerung: In der Zusammenfassung der Ergebnisse der VIVA-Studie werden wichtige wissenschaftliche Erkenntnisse zur Therapietreue ermittelt, die gegebenenfalls in die Empfehlung für pharmakologische Behandlungen eingehen.

Introduction

Osteoporosis presents significant costs to society. Estimates suggest every third woman and every fifth man over the age of 50 will suffer an osteoporosis related fracture (1, 2). In the first year after a hip fracture, the mortality rate is approximately 20 % (3). Estimates (4) showed that in 2009 the costs of osteoporosis in Germany were approximately 5.4 billion euros, although only 15 % of this total cost was due to medication. The greatest cost factor in osteoporosis is generated by the management required after fracture and thus the goal of treatment is to reduce the incidence of such fractures.

A number of medications exist for the treatment of osteoporosis. Bisphosphonates represent the current "gold standard medication" for osteoporosis treatment. For example, clinical studies have shown that implementation of ibandronate in post-menopausal women with osteoporosis reduced the risk of vertebral fracture by 62 % over a three-year observation period and reduced the risk of non-vertebral fractures in high-risk patients (femoral neck T-score < –3.0) by 69 % (5). However, the effects achieved in controlled clinical studies are not necessarily achieved in clinical practice.

The persistence and compliance of the patient with treatment is critical to the effectiveness of medication-intervention in osteoporosis (6–9). We define compliance as the patient taking the medication as directed, such as with or without food or at a certain time in the day, and persistence as the patient continuing to take medications, be it correctly or incorrectly, for the recommended period (6). Compliance can be a particular problem in patients prescribed oral bisphosphonates and this appears to be an even greater problem when the medication needs to be taken more frequently (10, 11). Recent reports on persistence with therapy in Germany (12, 13) indicate that after 12 months persistence with oral bisphosphonate therapy declined to well below 50 %. Poor compliance with oral bisphosphonates is in part due to the restrictions placed on the individual when it is to be taken: fasting, 30–60 minutes wait before eating and maintaining the upper body in an upright position for one hour afterwards.

Intravenous ibandronate (Bonviva®) has been available since 2006. In an earlier study (14) three milligrams ibandronate was injected every three months and compared to oral ibandronate taken daily in postmenopausal women with osteoporosis and a significantly greater improvement in bone mineral density over two years occurred in the intravenous regime. This finding may in part be due to the treating doctor having more control over the medication regime with a subsequent better compliance. Another factor may be that intravenous ibandronate avoids the poor resorption via the gut of ibandronate taken orally. As a randomized double-blinded controlled trial, this prior study (14) may not reflect the implementation of intravenous ibandronate treatment in clinical practice.

The goal of the "VIVA" (intravenous ibandronate versus oral alendronate) study was to examine the compliance and persistence of osteoporotic women with treatment in a non-interventional clinical setting. Patients whose treating doctor prescribed alendronate weekly were compared to patients whose treating doctor prescribed quarterly intravenous ibandronate. Here we present the methodology and baseline subject characteristics of the VIVA-study.

Materials, methods and patients

Ethical approval and recruitment process

Ethical approval was obtained from the institutional review board of each participating centre. All subjects gave their informed written consent and the study was conducted in accordance with the principles of the Declaration of Helsinki. Inclusion criteria were female gender, post-menopausal and diagnosis of osteoporosis.

Recruitment began in March 2010 and the final subject completed the 12-month observation period in December 2011. Patients were recruited from 458 private practices and five hospitals throughout Germany. The treating medical doctor was most often an orthopedic surgeon (60.04 % of a total of 463 medical doctors), general practitioner (28.51 %) or physician (13.17 %). Representatives of Roche Pharma AG informed and recruited medical doctors for study. According to paragraph 19 of the "voluntary self-control code for the pharmaceutical industry" (FSA-Kodex; http://www.fs-arzneimittelindustrie.de/) the practice visits by Roche Pharma AG regarding the study did not involve any advertising for Roche Pharma AG products.

Table 1 Subject characteristics

Parameter	Matched-pairs		Entire collective	
	Ibandronate i. v.	Alendronate	Ibandronate i. v.	Alendronate
Number of subjects	901	901	4477	1491
Age (years)	71.8 (9.3)	71.7 (9.3)	72.8 (9.3)	72.3 (9.0)
Height (cm)	162 (7)	162 (7)	161 (7)*	162 (7)
Weight (kg)	67.1 (11.4)*	68.9 (10.8)	66.7 (11.3)†	69.0 (11.9)
BMI (kg/m²)	25.6 (4.1)	26.2 (4.0)	25.6 (4.1)	26.3 (4.4)
Years post menopause	20.1 (10.7)	20.9 (10.4)	21.3 (10.9)	21.4 (10.4)
Years since osteoporosis diagnosis	3.1 (4.9)‡	2.9 (5.3)	4.0 (5.1)†	3.2 (5.3)
Analgesia use	48.6 %	44.7 %	45.4 %	43.2 %

*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$ and indicate significance of difference between groups. Analgesia use reports the percentage of subjects taking medication for osteoporosis related pain.

Justification of sample size and participant characteristics

Clinical experience prior to initiation of the study suggested that patients would be more likely to receive quarterly ibandronate 3 mg i.v. than alendronate weekly if they had gastrointestinal problems, prevalent fractures, multiple diseases and/or dementia. It was therefore necessary to design the study to enable the generation of matched-pairs at study conclusion. We therefore aimed to recruit patients to ensure a ratio of 3:1 ibandronate i.v.: alendronate oral. We estimated that this would ensure 90% of the alendronate patients had a matched-pair in the ibandronate group. Subsequently, pairs could be matched according all of the following criteria: age, body mass index, fracture history at study inclusion, whether or not the patient had prior treatment with bisphosphonates and the number of concomitant disorders.

In order to be able to detect an effect-size of 5% in the persistence with treatment between two groups with a power of 80% and an alpha-level of 0.05, it was required to include 360 patients per group (calculated with Program N from IDV Gauting, Munich, Germany). The primary goal of the study was the assessment of persistence with therapy of quarterly ibandronate i.v. versus weekly alendronate orally. Two additional goals of this study were to examine the factors, such as age and health status that impact upon persistence with therapy as well as the impact of therapy persistence on patient pain, quality of life, mobility and new osteoporotic fracture. Thus, for these three separate goals, 1080 patients would have been required. Assuming 90% of the alendronate patients would have a matched-pair in the ibandronate group with given a 3:1 ratio of ibandronate:alendronate patients, and further assuming a 20–25% drop-out rate, it would be necessary to include 1500 alendronate oral patients and 4500 ibandronate i.v. patients in the study.

At the completion of recruitment, 4477 patients receiving ibandronate 3 mg i.v. quarterly and 1491 patients receiving alendronate 70 mg orally weekly were included in the study (▶Table 1).

Table 2 DXA in the six months prior to inclusion

Parameter	Matched-pairs		Entire collective	
	Ibandronate i.v.	Alendronate	Ibandronate i.v.	Alendronate
Lumbar spine (L1–4)				
T-score	–2.9 (1.0)	–2.9 (1.0)	–3.0 (0.9)	–2.9 (1.0)
N	573	608	2837	955
Total hip				
T-score	–2.4 (0.9)	–2.4 (0.9)	–2.4 (0.9)	–2.3 (0.9)
N	461	507	2301	773

N: number of subjects with dual X-ray absorptiometry scans in the 6-months prior to inclusion in the study. No significant differences between groups.

Study conduct

This study was a non-interventional study. Thus, the treating medical doctor made an independent decision regarding treatment modality before inclusion in the study. If the medical doctor implemented treatment with either ibandronate 3 mg i.v. or alendronate 70 mg weekly, then the treating doctor informed the patient regarding the study. If the patient agreed to inclusion in the study and gave their informed written consent, patient status at baseline was then recorded. Patients could return for optional visits in accordance to the local requirements and were asked to attend a final 12-month visit.

At inclusion into the study the following information was recorded: date of examination, unique patient identifier (assigned by treating doctor), date of birth, height, weight, gender, time since menopause, date of first diagnosis of osteoporosis, radiological method used for diagnosis (DXA), concomitant disorders, osteoporosis risk factors as indicated by the DVO guidelines 2009, prior and current medication, results of dual X-ray absorptiometry scanning in the last six months (if available), osteoporosis related fractures prior to inclusion in the study, osteoporosis related mobility restriction (classified by the medical doctor as: "none", "little", "moderate", "large" or "very large"), health related quality of life and satisfaction (chosen by patient from: "very satisfied", "satisfied", "neither satisfied nor dissatisfied", "dissatisfied", "very dissatisfied"), osteoporosis related pain (chosen by the patient as: "none", "little", "moderate", "strong" or "very strong" and also quantified via a visual analogue scale [VAS] [15]), analgesics in the last seven days, start date of current osteoporosis therapy, prior osteoporosis medication, side effects of treatment. Subjects also completed questionnaires on health status

Table 3 Prior osteoporotic fracture

Parameter	Matched-pairs		Entire collective	
	Ibandronate i.v.	Alendronate	Ibandronate i.v.	Alendronate
Vertebral body	24.5%	24.5%	34.2%‡	27.8%
Femoral neck	3.2%	4.0%	3.9%	4.0%
Radius	7.7%	7.3%	8.0%	7.8%
Other	8.3%	6.9%	10.1%*	8.1%
All osteoporotic fractures	36.6%	35.7%	45.7%‡	39.9%

Data are percentage of total subjects in each group. N = 4476 for the ibandronate i.v. "entire collective", otherwise number of subjects as per Table 1. *$p < 0.05$; ‡$p < 0.001$ and indicate significance of difference between groups.

(SF-12 [16]) and tools for the prospective assessment of probable compliance: the "sensorimotor amplification scale" (SSAS; a measure of perceived sensitivity to several unpleasant bodily sensations [17]) and the "beliefs about medicines questionnaire" (BMQ; a self-report tool for screening compliance and barriers to compliance [18]).

At 12-months, the following information was recorded by the medical doctor: date of examination, patient height, whether the patient is still receiving the same treatment, when treatment with medication was ended (if applicable), reason for ending treatment (if applicable), amount of medication prescribed or injected, any new osteoporosis related fractures, osteoporosis related mobility restriction, osteoporosis related pain, change in analgesic use, compliance with alendronate therapy (via prescription control) and side-effects of therapy since last examination. Patients were given three questionnaires (SF-12, SSAS, BMQ) for them to complete at home and we asked to send them to the study coordinator (factum GmbH, Offenbach, Germany).

Data were entered by the medical doctor, or their authorized representative, into a secure online portal. The data were anonymized with each medical doctor assigning their own unique identifier for the patient in the online portal. The connection between patient number and personal details was known only to the treating doctor or their authorized representative.

Outcome measures

In this manuscript, we present the baseline characteristics of the entire collective of patients as well as the matched pairs for subject demographic and anthropometric characteristics, results of DXA measurement in the last six months (number with measurement and T-scores), osteoporosis related fractures at baseline, osteoporosis related mobility restriction, health related quality of life, osteoporosis related pain, analgesia use at baseline, physical and mental health composite scores from the SF-12 questionnaire, summary score from the "sensorimotor amplification scale" and the scales for medication usage, harmfulness and usefulness from the "brief medication questionnaire".

Compliance was defined as the number of tablets taken/number of injections over 12 months. Persistence was defined as the proportion of patients who remained on the prescribed medication for 12 months. The percentage of patients with a persistence rate of ≥75% was determined in each group.

Statistical analyses

For comparisons between the two groups at baseline of continuous variables, the independent samples median test was used. For categorical data, chi-square tests were used. An alpha level of 0.05 was used for statistical significance. Statistical analyses were performed with SPSS (version 15.0, http://www-01.ibm.com/software/analytics/spss/). The statistical analyses were conducted by factum GmbH (Offenbach, Germany). Unless otherwise stated, values are reported as mean (SD). Where the numbers of subjects available for certain parameters differ from the collectives given in ▶Table 1, this is stated.

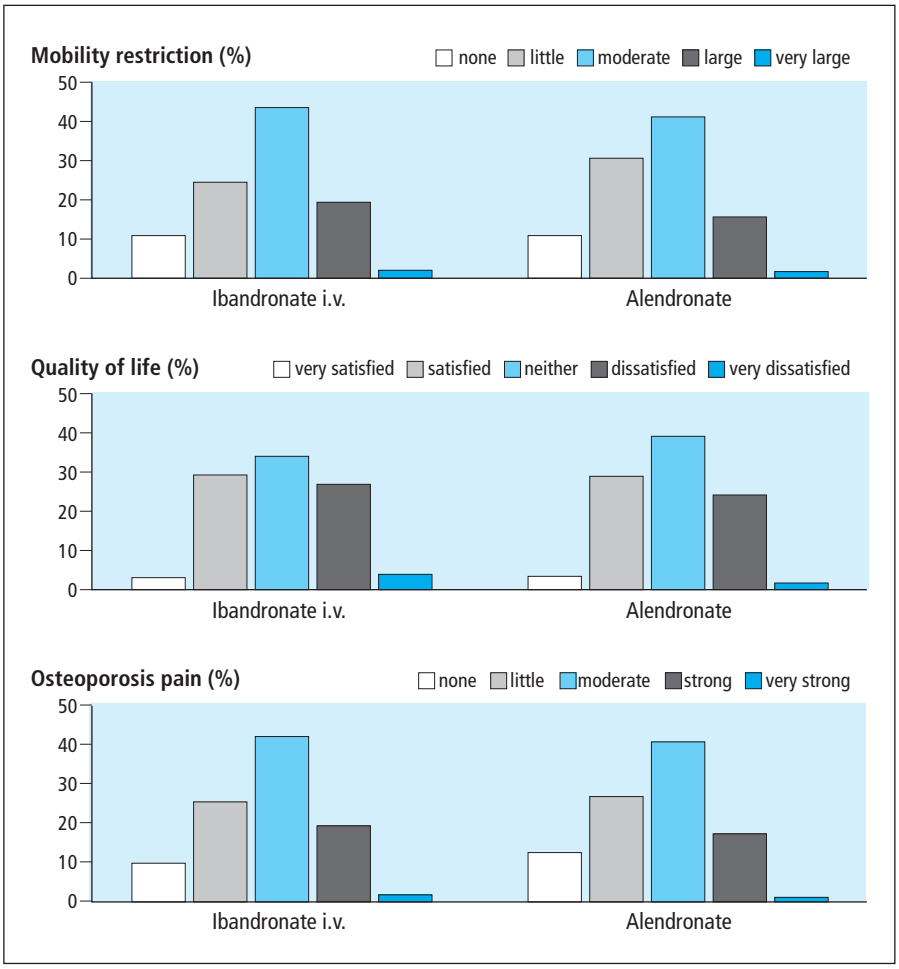

Fig. 1 Mobility, quality of life and pain in the entire collective. No significant differences between groups.

Results

When considering the entire collective, patients in the ibandronate i.v. group weighed significantly less, had a current diagnosis of osteoporosis for a significantly longer duration than the alendronate-group (▶Table 1). Otherwise no differences were apparent between groups for age, BMI, years since menopause and analgesia usage (▶Table 1). DXA scores did not differ between the groups (▶Table 2).

The ibandronate i.v. group had a higher incidence of prior osteoporotic fracture in the vertebral body and in regions other than the vertebral body, femoral neck and radius (▶Table 3). Mobility restriction and quality of life (▶Fig. 1) as well as SF-12 scores, the sensorimotor amplification scale, and attitudes towards medication as captured with the BMQ (▶Table 4) at baseline were similar in both groups.

When the matched-pair groups were considered, the differences between groups in fracture incidence were no longer apparent (▶Table 3). Mobility restriction and quality of life were significantly worse in the matched pairs ibandronate i.v. group (▶Fig. 2). Otherwise the results were similar as when the entire collective was considered.

Table 4 SF-12, SSAS and BMQ questionnaire

Parameter	Matched-pairs		Entire collective	
	Ibandronate i.v.	Alendronate	Ibandronate i.v.	Alendronate
SF-12				
Physical health composite score	34.5 (10.0)	34.7 (9.9)	34.4 (9.8)	34.8 (9.8)
Mental health composite score	45.0 (11.1)	45.5 (11.6)	45.6 (11.2)	45.4 (11.5)
N completed	40.3 %	37.4 %	37.9 %	38.2 %
Sensorimotor amplification scale (SSAS)				
Summary score	29.6 (6.5)	30.2 (6.7)	29.9 (6.6)	29.9 (6.9)
N completed	38.3 %	35.5 %	36.0 %	36.4 %
Brief medication questionnaire (BMQ)				
Medications are...				
...used excessively	13.0 (3.0)	12.8 (3.1)	12.9 (3.1)	12.8 (3.2)
...harmful	10.3 (3.0)	10.4 (3.1)	10.2 (3.0)	10.4 (3.3)
...useful	16.0 (2.4)	15.8 (2.4)	16.0 (2.4)	15.8 (2.5)
N completed	59.8 %	62.9 %	62.2 %	62.0 %

N = percentage of subjects who returned a completed questionnaire. No significant differences between groups.
Interpretation of SF-12 scores: the questionnaire is designed such that a score of 50 indicates „average" health. A score of 40 is one standard deviation below the average (i.e. 84 % of the population with better health) and a score of 30 is two standard deviations below the mean (i.e. 98 % of the population with better health).
Interpretation of SSAS scores: German normative data (unpublished observations in 2512 individuals) give a mean value of 27.6 with a higher score implying increased sensitivity to unpleasant bodily sensations.
Interpretation of BMQ scores: German normative data (unpublished observations in 2512 individuals) give a mean value of 14.6 for excessive use, 11.0 for harmfulness and 15.7 for usefulness. Lower scores imply a belief that mediations are not used excessively, are not harmful or not useful.

Discussion

Any clinical benefits of a medication found in randomized controlled trials can only be transcribed into clinical practice if the medication is taken as it is prescribed. Thus an important aspect of examining efficacy of any medication is whether patients adhere to the treatment schedule. Hence, the goal of the VIVA study was to examine, in a non-interventional clinical setting, the compliance and persistence of patients with osteoporosis with treatment with quarterly intravenous ibandronate versus weekly alendronate taken orally.

Several aspects of the study design are noteworthy. First, the VIVA study is testing compliance and persistence of patients with postmenopausal osteoporosis to a pharmacological treatment regime in a real world setting. The effectiveness of both bisphosphonate (6) and ibandronate therapy (15) has been studied in controlled clinical trials. However, the current study is the first to test compliance and persistence with intravenous ibandronate in a direct head to head comparison to oral alendronate on a large scale. Some prior data are available for oral bisphosphonates and these indicate that after 12-months, persistence with treatment drops below 50 %.

Secondly, questionnaires (SSAS and BMQ) were implemented to prospectively estimate the likely adherence of the patient with therapy. This will then be compared to actual compliance and persistence data. In so doing, the results of this study will provide an additional tool for choosing suitable therapy approaches for different patient collectives. Further planned analyses examining the association of subject characteristics (such as age and health status) and therapy persistence will also help to guide clinical practice in determining which patients are most likely to benefit from which therapeutic approaches.

Third, the VIVA study will give evidence of whether ibandronate i.v. and oral alendronate differ in clinical practice in their impact upon pain, analgesia use, quality of life, mobility and incidence of osteoporotic fractures. This information is critical for assessing the „real life efficacy" of these pharmacological interventions for postmenopausal osteoporosis.

Results from the VIVA study should influence policy pertaining to implementation of pharmacological interventions in the clinical management of patients with postmenopausal osteoporosis. Based upon current guidelines (5) and given the characteristics of a typical patient in our collective (postmenopausal, 72 years old, lumbar T-score –2.9, total hip T-score –2.4, moderate osteoporosis pain and moderate mobility restriction) pharmacological intervention would include bisphosphonates, selective estrogen receptor modulators as well as strontium ranelate. If persistence differs between the study arms, the VIVA study will help to show how these recommen-

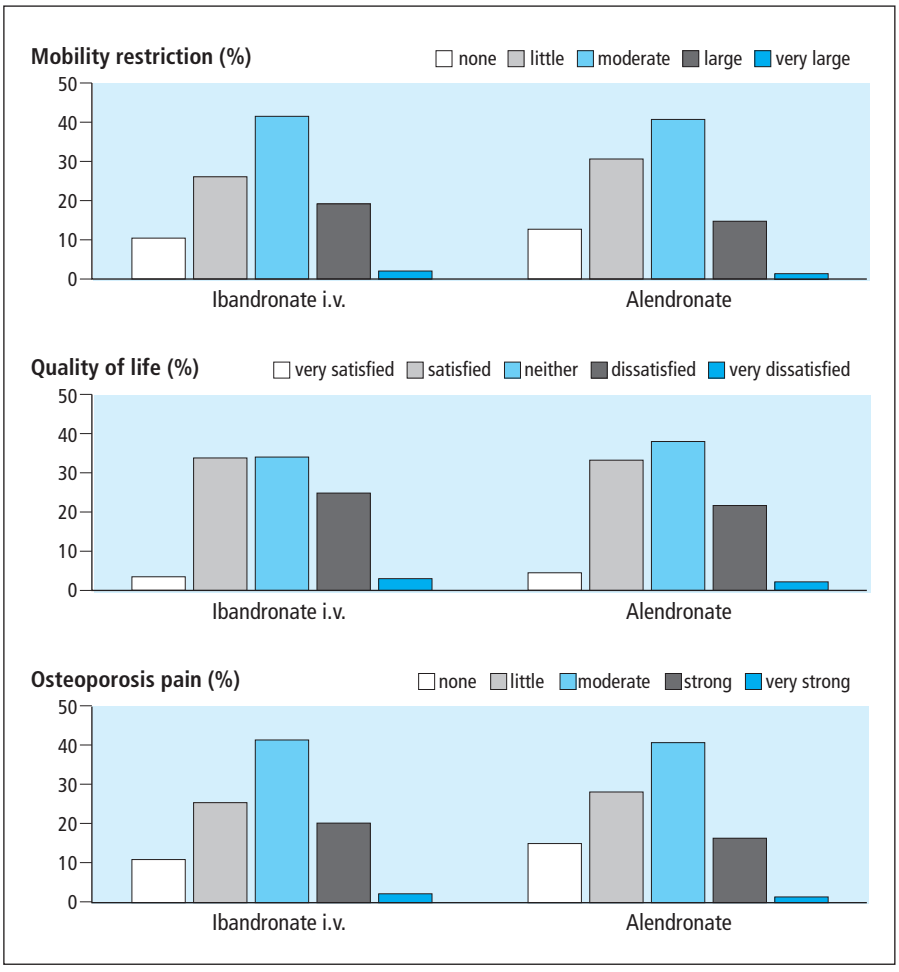

Fig. 2 Mobility, quality of life and pain at the start in the matched-pairs collective. Mobility restriction ($p < 0.05$) and quality of life ($p < 0.01$) differed between groups.

dations can best be translated into clinical practice and may result in changes in treatment guidelines.

The design of the VIVA-study has some potential limitations. An additional placebo group is not planned, which will impede the interpretation of results on efficacy. Also, it will not be possible to assess whether subjects actually implement the correct method of administration of the alendronate tablets. Although it is very difficult to design studies to assess this aspect of compliance, this dimension of compliance will nonetheless not be captured. Furthermore, the ibandronate i.v. group had, at baseline, a higher incidence of prior osteoporotic fractures and also a longer duration of the diagnosis of osteoporosis. Available data suggest that this could be associated with a greater severity of osteoporosis (19), potentially impeding the assessment of efficacy and also reduce compliance (20).

Conclusion

In conclusion, results from the VIVA study will provide the scientific rationale for routinely implementing either quarterly ibandronate intravenously versus a bisphosphonate to treat postmenopausal osteoporosis.

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Conflict of interest

Peyman Hadji has acted as a consultant and speaker for Amgen, Elli Lilly, Nycomed, Roche, Novartis, Procter and Gamble and MSD but has not received royalties from the companies.
Lorenz Hofbauer has acted as a consultant and speaker for Amgen, Nycomed, Novartis, and MSD but has not received royalties from the companies.
Dieter Felsenberg has acted as a consultant and speaker for Roche, Novartis, Procter and Gamble and MSD but has not received royalties from the companies.
Michael Amling has acted as a consultant and speaker for Roche, Novartis, Procter and Gamble, MSD, Servier, and Lilly but has not received royalties from any company.
Andreas Kurth acted as a speaker for Roche and is active on the advisory board for Bonviva. He is also a speaker for Biomet, Dfine Europe, Medtronic, Servier, Novartis, Lilly, Amgen, BMS, GSK, Baxter, Boehringer Ingelheim, Anwerina and a consultant for Dfine Europe, Biomet, Servier, Amgen, Boehringer Ingelheim, BMS.

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