VIBE: Evaluation of Ibandronate Efficacy

A Retrospective Cohort Study Comparing Fracture Rates For Women Receiving Monthly Ibandronate vs Weekly Bisphosphonates

Presentation of a Sub-Group Analysis Excluding Patients with Osteopenia, Alendronate 35mg and Corticosteroid Use

VIBE: İbandronat'ın Etkinliğinin Değerlendirilmesi

Haftalık Bifosfonatlar ve Aylık İbandronat Tedavisinde Kadınlarda Kırık Oranlarını Karşılaştıran Rretrospektif Bir Kohort Çalışması

Osteopenik, Alendronat 35 mg ve Kortikosteroid Kullanımı Olan Hastaları Dışlayan Bir Alt Grup Analizinin Sunulması

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Summary

No prospective head-to-head trials comparing the fracture efficacy of the currently marketed weekly and monthly bisphosphonates have been conducted. Due to the large sample size such studies would require to reliably detect differences in fracture risk and the associated high costs, they are considered to be impractical. Whilst providing the highest level of evidence, clinical trials also have inherent limitations. Patients are selected by a number of criteria and therefore usually do not represent the normal patient population. Also due to a protocol, normal clinical practice is usually not reflected. In contrast, database studies allow the assessment of treatments in normal clinical practice. Whilst observational studies have limitations owing to more confounding variables, they do have an important place in evidence-based medicine (especially in the absence of prospective clinical trials), and if well-designed can give some indications regarding the comparative efficacy of osteoporosis therapies in real-world clinical practice. *(From the World of Osteoporosis 2008;14: 62-5)*

Key words: Efficacy, Ibandronate

Özet

Haftalık ve aylık uygulanan bifosfonatların kırıklar üzerindeki etkinliğini bire-bir [head-to-head] karşılaştıran prospektif çalışmalar yapılmamıştır. Kırık riskindeki farklılıkları güvenilir biçimde saptamak için gerek duyulacak büyük örneklem boyutu ve bununla ilişkili yüksek maliyetlerden ötürü, bu gibi çalışmaların pratik olmadıkları kabul edilmektedir. En yüksek düzeydeki kanıtları sağlamakla birlikte, klinik çalışmaların da çalışmanın özelliğinden kaynaklanan kısıtları vardır. Hastalar bir dizi kritere göre seçildiğinden, çoğunlukla normal hasta popülasyonunu temsil etmemektedirler. Ayrıca, uygulanan protokol, normal klinik uygulamayı genellikle yansıtmamaktadır. Buna karşılık, veri tabanı çalışmaları normal klinik uygulamadaki tedavilerin değerlendirilmesine imkan vermektedir. Gözlemsel çalışmaların, daha fazla çeldirici değişken içermelerinden ötürü kısıtları olmasına karşın, bunlar kanıta-dayalı tıpta önemli bir yere sahiptir (özellikle prospektif klinik çalışmalar bulunmadığında) ve eğer iyi tasarlanmışlarsa, gerçek dünyada klinik uygulamadaki osteoporoz tedavisinde karşılaştırmalı etkinliğe dair bazı göstergeler sağlayabilirler. *(Osteoporoz Dünyasından 2008;14: 62-5)*

Anahtar kelimeler: İbandronat, etkinlik

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VIBE Study

The VIBE (EValuation of IBandronate Efficacy) study was a retrospective study of women ≥45 years taking once monthly BONVIVA 150mg (n=7,345) or weekly alendronate 35mg/70mg (n=35,865) or risedronate 35mg (n=20,972).

The study used eligibility, pharmacy claims and medical claims from research databases in the US. There are important differences in the treatment and management of osteoporosis in the US and Europe, so to create a population that was more reflective of bisphosphonate labels in Europe, the following were excluded:

- patients with osteopenia
- glucocorticoid use
- alendronate 35mg

Here we present the results of the analysis of this osteoporotic sub-group which included 41,858 patients (Bonviva n=4,876, alendronate n=22,805, risedronate n=14,177).

Objective Methods

Objective

To investigate the anti-fracture efficacy of once monthly oral Bonviva versus weekly bisphosphonates by comparing rates of incident clinical fractures over 12 months in osteoporotic patients in a retrospective observational study.

Study Design

The VIBE study was a retrospective claims database study, which used eligibility, pharmacy claims and medical claims data from the i3 research database (includes data from a large US health plan affiliated with i3 Innovus) and the i3 IMPACT database (includes data from 45 unaffiliated health systems).

Statistical analyses

Fracture rates were compared using time-to-event analysis with Cox proportional hazard models to estimate the relative risk (hazard rate) of fracture for monthly ibandronate versus weekly bisphosphonates (BPs), controlling for potential confounding factors.

Patients

- Women ≥45 years of age
- Newly prescribed monthly oral ibandronate or weekly oral bisphosphonates (alendronate 70mg, or risedronate 35mg) between 1 April 2005 and 31 December 2005
- Eligible patients had continuous health plan eligibility for 6 months prior to the index date (pre-index period), and at least 3 months after the index date (post-index period)
- Excluded women if they were prescribed a bisphosphonate during the pre-index period, had malignant cancer (ICD-9-CM codes 140.xx – 208.xx) during the pre-index period, or Paget's disease (ICD-9-CM code 731.0) at any time during the study

Baseline Characteristics Table 1

Period of Observation

Each subject was required to have a 6 month baseline period to examine medication use and medical history. After starting bisphosphonate therapy each subject was observed for fracture for up to 12 months, or until:

- Loss to follow-up (end of health plan enrolment)
- Discontinue therapy (for primary analysis only)
- Change in bisphosphonate therapy
- Switch to a different bisphosphonate
- Switch dosing regimen (e.g. weekly to daily)

Results

The sub-analysis included 41,858 patients with primary osteoporosis (Bonviva n=4,876, weekly n=36,982) Table 2.

Results suggested patients treated with Bonviva had

- Comparable fracture rates at non-vertebral sites and the hip compared to weekly bisphosphonates
- Statistically significantly lower rates of vertebral fractures compared to weekly bisphosphonates

Time to Fracture

Crude fracture rates using Kaplan-Meier method

Excluding patients with osteopenia, alendronate 35mg or corticosteroid use.

Table 1. Baseline Characteristics

	Monthly İbondronate (n=4,876)	Weekly BP therapy (n=36,982)	p-value
Duration of observation in days, mean (SD)	222.49 (94.09)	215.34 (98.22)	<.0001
Age, mean (SD)	60.80 (8.80)	61.43 (9.04)	<.0001
Osteoporosis diagnosis	52.77%	47.30%	<.0001
Bone densitometry procedure	48.97%	47.21%	0.0207
Fracture history	3.71%	3.88%	0.5727
Gastrointestinal diagnosis	22.07%	15.85%	<.0001
Gastrointestinal medication use	22.91%	15.55%	<.0001
Estrogen use	23.48%	17.56%	<.0001
Other anti-osteoporotic use	11.67%	6.32%	<.0001
Number of therapeutic classes, mean (SD)	5.45 (4.39)	4.60 (3.91)	<.0001
Outpatient visits, mean (SD)	14.82 (15.44)	13.79 (16.17)	<.0001
Hospitalisation	4.66%	5.17%	0.1232

Discussion-usefulness of observational studies

No prospective head-to-head trials comparing the fracture efficacy of the currently marketed weekly and monthly bisphosphonates have been conducted, due to the large sample size such studies would require to reliably detect differences in fracture risk, and the associated high costs (1). Furthermore, clinical trials have limitations including restricted 'generalisability.' Patient populations, treatment patterns and patient outcomes in normal clinical practice may differ from randomised clinical trials, so it is useful to assess outcomes in real-world settings.

Observational studies provide valuable data complementary to the information provided by randomised clinical trials (2). These sorts of studies allow analyses of large sample sizes which are necessary to compare anti-fracture efficacy of osteoporosis treatments. Finally, with observational studies, you avoid the influence of trial participation on outcomes, and allow the evaluation of agents in a population with a broader range of characteristics (versus those typically permitted in a randomised clinical trial).

Whilst these advantages are important considerations when interpreting the VIBE study, there are disadvantages which are inherent in any observational database study. Firstly, the data were collected for the purposes

Table 2.

Fracture type	Patients with fracture, n (%)		Unadjusted relative risk[a]	Adjusted relative risk (95% CI)[b]	p
	Weekly BPs	Monthly ibandronate			
Vertebral	93 (0.25)	6 (0.12)	0.47	0.40 (0.17–0.92)	0.031
Hip	71 (0.19)	11 (0.23)	1.12	1.35 (0.71–2.57)	0.359
Nonvertebral	484 (1.31)	66 (1.35)	0.99	0.93 (0.72–1.21)	0.586
Any clinical	565 (1.53)	72 (1.48)	0.93	0.86 (0.67–1.11)	0.247

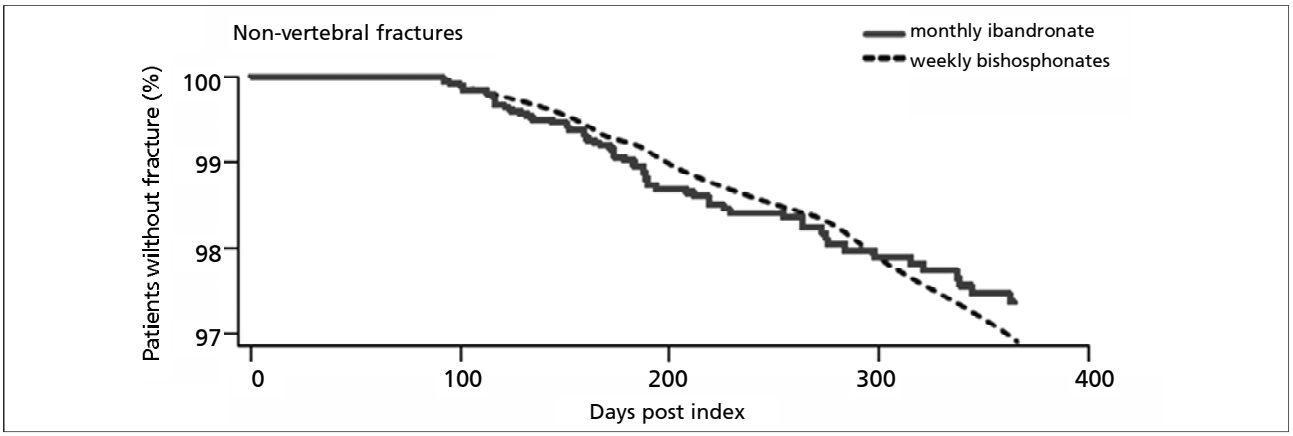

Figure 1.

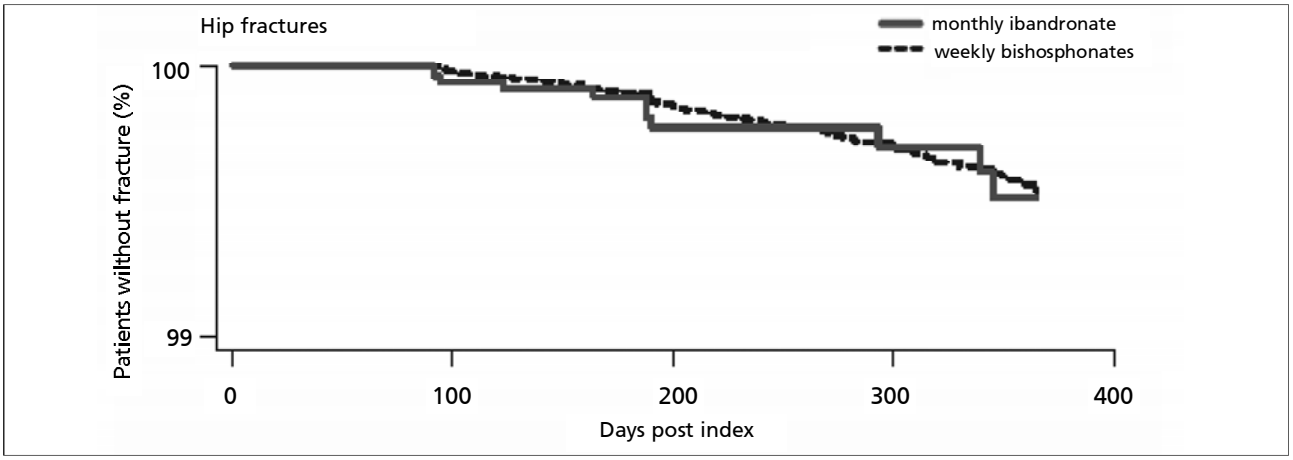

Figure 2.

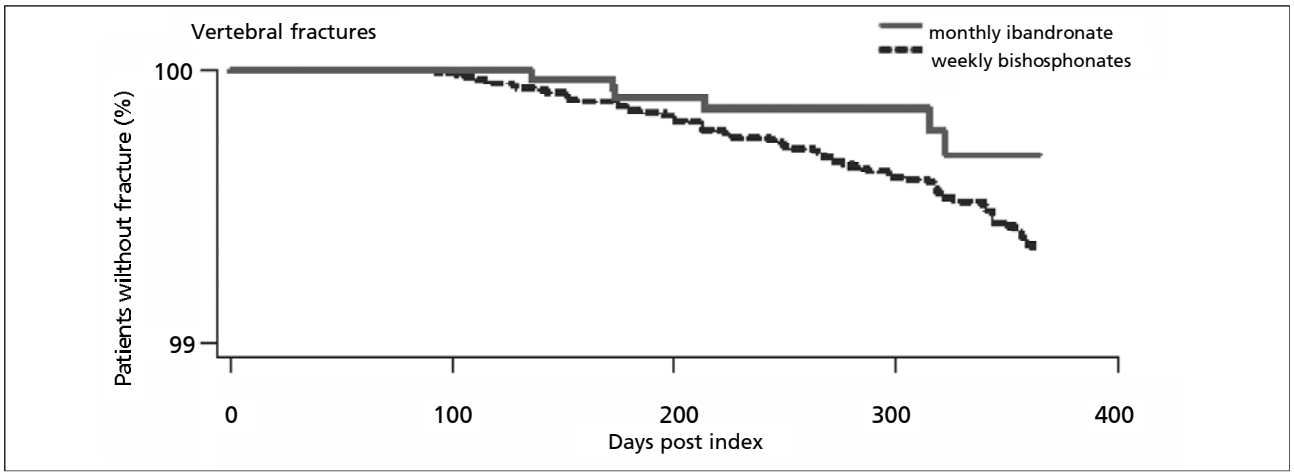

Figure 3.

of reimbursement, not research, so this is associated with certain limitations. For example, the presence of a claim does not indicate that the medication was taken or taken correctly, and no data are available on samples provided by physicians.

Additionally, the presence of a diagnosis code does not necessarily indicate presence of the disease (the diagnosis may have been incorrectly coded). It is also important to consider that, in real-life clinical practice settings, treatment selection may be influenced by factors which are not recorded in the database. Data were available on the use of dual-energy x-ray absorptiometry (DXA), but not on the results. Vertebral fracture diagnoses were not validated by evidence of a spinal x-ray; however, it is likely that any misclassification occurred to the same extent in the monthly Bonviva and weekly bisphosphonate groups. Data were not available on fractures that occurred before the pre-index period, or on other fracture risk factors such as smoking or alcohol use. The analysis controlled for known baseline characteristics; however, it is possible that there were unidentified baseline differences between groups that could not be accounted for. Also, p-values were not adjusted for multiple comparisons.

In summary, findings from observational database studies, although potentially subject to more confounding, have an important place in evidence-based medicine as they provide valuable insight into the real-world use of treatments. If well-designed, these sorts of studies can give some indications regarding the comparative efficacy of osteoporosis therapies in real-world clinical practice.

Conclusions

This sub-group analysis from the VIBE study found that in a real-life clinical setting, following one year's treatment, the risk of hip fractures or non-vertebral fractures was similar in patients who received monthly ibandronate or weekly bisphosphonates. This suggests that monthly Bonviva has similar non-vertebral and hip anti-fracture efficacy as the weekly bisphosphonates, alendronate and risedronate. (Note: efficacy on femoral neck fractures or non-vertebral fractures has not been prospectively established with ibandronate).

The rate of vertebral fractures was statistically significantly lower in adherent patients treated with monthly Bonviva compared with weekly bisphosphonates. The clinical implications of these findings need further exploration and validation. In the additional sensitivity analyses conducted (such as the analysis of patients ≥65 years and exclusion of baseline characteristics known to influence fracture risk such as gastrointestinal medication, fracture during baseline period) these findings were consistent.

References

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