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Effect of Monitoring Bone Turnover Markers on Persistence with Risedronate Treatment of Postmenopausal Osteoporosis

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Context: Persistence with osteoporosis treatment is poor but is important for maximum benefit.

Objective: The objective of the study was to assess the impact of physician reinforcement using bone turnover markers (BTMs) on persistence with risedronate treatment.

Design and Setting: This was a 1-yr multinational prospective, open-label, blinded study in 171 osteoporosis centers in 21 countries.

Patients: A total of 2382 postmenopausal women (65–80 yr old) with spine/hip T-score −2.5 or less or T-score −1.0 or less with a low-trauma fracture.

Intervention: Intervention included calcium 500 mg/d, vitamin D 400 IU/d, and risedronate 5 mg/d for 1 yr. Centers were randomized to reinforcement (RE+) or no reinforcement (RE−). At 13 and 25 wk, reinforcement based on urinary N-telopeptide of type I collagen change from baseline was provided to the RE+ patients using the following response categories: good (>30% decrease), stable (−30% to +30% change), or poor (>30% increase).

Main Outcome Measures: Persistence assessed with electronic drug monitors was measured.

Results: In the overall efficacy population (n = 2302), persistence was unexpectedly high and was similar for both groups (RE−, 77%; RE+, 80%; $P = 0.160$). A significant relationship between the type of message and persistence was observed ($P = 0.017$). Compared with RE−, intervention based on a good BTM response was associated with a significant improvement in persistence [hazard ratio (HR) 0.71; 95% confidence interval (CI) 0.53–0.95]. Persistence was unchanged (HR 1.02; 95% CI 0.74–1.40) or lower (HR 2.22; 95% CI 1.27–3.89) when reinforcement was based on a stable or poor BTM response, respectively. Reinforcement was associated with a lower incidence of new radiologically determined vertebral fractures (odds ratio 0.4; 95% CI, 0.2–1.0).

Conclusions: Reinforcement using BTMs influences persistence with treatment in postmenopausal women with osteoporosis, depending on the BTM response observed. (***J Clin Endocrinol Metab* 92: 1296–1304, 2007**)

OSTEOPOROSIS IS underdiagnosed and undertreated, with patients often identified after fracture (1). Worldwide, approximately 200 million women have osteoporosis (2). In the United States alone, 10 million people have osteoporosis, and 34 million more have low bone mass (3).

Poor compliance and persistence with long-term treatment are major obstacles in the management of osteoporosis because they are for other chronic diseases (4, 5). One-year compliance is 50–70% for antihypertensives (6, 7) and 25–40% for statins (8, 9). Similarly, compliance is poor with osteoporosis therapies, ranging from less than 25% to around 75% at 1 yr (10–13), with mean persistence around 245 d (13). In an analysis of a managed care claims database, 48% of patients did not fill a second 30-d prescription (14). Poor adherence results in reduced therapeutic efficacy (10, 15) and has economic consequences (16).

Bone turnover markers (BTMs) have been used to assess fracture risk and monitor response to osteoporosis treatment (17). Decreases in BTMs after 3–6 months of antiresorptive therapy predict subsequent reduction in fracture risk (18–21). We hypothesized that assessment of changes in BTMs would be a useful tool to improve patient persistence.

The Improving Measurements of Persistence on Actonel Treatment (IMPACT) study was designed to investigate the effect of early reinforcement, based on changes in BTMs, on persistence with risedronate treatment and identify factors that influence persistence.

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* Names of IMPACT investigators are listed in Appendix A, published as supplemental data on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org.

Abbreviations: AE, Adverse event; BMD, bone mineral density; BTM, bone turnover marker; CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; IMPACT, Improving Measurements of Persistence on Actonel Treatment; ITT, intention to treat; SAE, serious AE; uNTX, urinary N-terminal cross-linking telopeptide of type I collagen.

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Patients and Methods

Study design

This 1-yr, multinational, prospective study was conducted between August 11, 1999, and February 5, 2002, at 171 centers in 21 countries, including Australia, North and South America, Europe, and Africa (Appendix A, published as supplemental data on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). The study used a cluster randomization design in which centers (clusters) were randomized into either reinforcement (RE+) or nonreinforcement (RE−).

The study included seven visits, which are detailed in Fig. 1. If patients were prematurely withdrawn from the study, a final visit was conducted according to the requirements of visit 7. Clinical data were recorded using an electronic case report form.

The study was conducted in accordance with the Declaration of Helsinki and approved by the appropriate institutional review boards. All patients provided written informed consent.

Patients

Eligible subjects were postmenopausal women aged 65–80 yr who had not been previously diagnosed with osteoporosis and who had either a bone mineral density (BMD) T-score −2.5 or less at the left hip or spine or a BMD T-score between −1.0 and −2.5 with a clinically documented low-trauma fracture sustained at or after age 45 yr. Patients were excluded if they had received systemic glucocorticoids at doses equivalent to prednisone greater than 5 mg/d for more than 1 month within 6 months before study entry, any glucocorticoid treatment within 3 months of study entry, or used any prior medications specifically for the treatment of osteoporosis. The majority of sites were hospital-based or academic clinics with specialties in osteoporosis. Patients were referred by primary care physicians or were recruited by mailing or advertisement.

Randomization and intervention

Randomization of centers was generated centrally, and reinforcement allocation was sent to the sites before the first patient was screened. Centers assigned to RE+ received urinary N-terminal cross-linking telopeptide of type I collagen (uNTX) results in graphic form and the appropriate message linked to that biological response for each BTM assessment. Centers assigned to RE− collected urine samples for NTX from subjects but did not have access to BTM information. Because sites rather than patients were randomized, all patients of the same center were allocated to the same group (RE+ or RE−). The median center size was 15 patients (range 1–40).

Calcium (500 mg/d) and vitamin D (400 IU/d) were initiated during the screening period, 2–4 wk (median, 20 d) before wk 0 when risedronate treatment was started, and continued throughout the study. All patients received oral risedronate 5 mg daily and were instructed to take their medication in an upright position with a minimum of 6–8 oz of water. Risedronate pills were enclosed in a bottle with an electronic monitor (MEMS; AARDEX, Zug, Switzerland) that recorded the date and time of tablet dispensation. The MEMS monitors were switched to a new bottle with risedronate tablets at wk 13 and 25. At wk 52, patients returned their study medication including their MEMS monitors and the data were downloaded to an electronic database.

At wk 13 and 25, all patients (RE− and RE+) received information about the need to continue treatment (Appendix B, see supplemental data). RE+ patients were given a paper copy of a graph of their uNTX results showing percent change. Messages were based on change from baseline in uNTX. We estimated the least significant change, using the average of two uNTX values, to be 30%. This was based on a coefficient of variation of 23%, a P value of 0.10, and a one-sided t test. Patients with more than 30% decrease in uNTX received reinforcement based on their good BTM response, patients between −30% and +30% change received reinforcement based on their stable BTM response, and patients with more than 30% increase received a message based on their poor BTM response. Apart from the BTM reinforcement provided to patients in RE+ centers, the study protocol and interventions were identical in RE+ and RE− centers.

Measurements

uNTX was measured in a central laboratory (Synarc, Lyon, France) at baseline and at wk 10 and 22 by ELISA using an automated analyzer (Vitros Eci; Ortho Clinical Diagnostics, Rochester, NY). Intraassay variation was 1.1–6.7% and interassay variation was 3.5–7.8%. Baseline uNTX levels were the mean of two second-void morning urine samples collected on consecutive days after the calcium/vitamin D run-in but before initiating risedronate treatment.

Lateral thoracic and lumbar spine x-rays were performed at study entry and again at 12 months. Because the final assessment was an amendment to the original protocol, only 57% (1317 of 2302) of the patients had x-rays evaluable for both time points. Vertebral fractures were assessed by both local radiologists according to the semiquantitative method described by Genant *et al.* (22) and were sent to a single central reading facility (Synarc, San Francisco, CA) for confirmation of radiographic quality and blinded assessment of vertebral fractures (23).

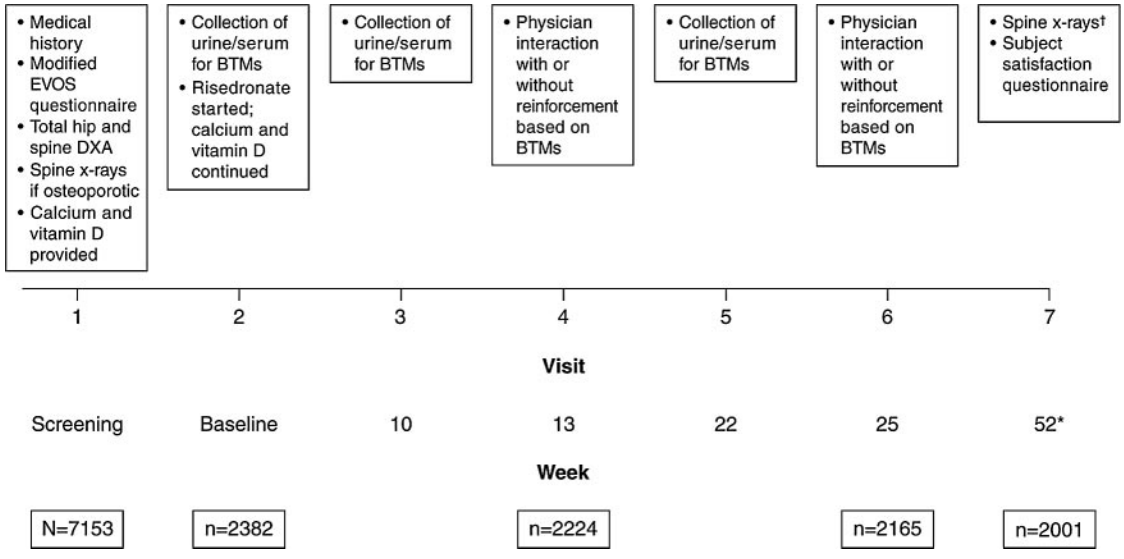

FIG. 1. Time line of study procedures. *, If patients were prematurely withdrawn from the study, a final visit was conducted according to the requirements of visit 7. †, Based on protocol amendment, final spine x-rays were evaluated in a subset of 1317 patients. EVOS, European Vertebral Osteoporosis Study; DXA, dual x-ray absorptiometry; BTM, bone turnover marker.

Nonvertebral fractures were recorded on the electronic case report form as adverse events. Nonvertebral osteoporotic fractures were defined as those occurring at six skeletal sites (clavicle, hip, humerus, leg, pelvis, and wrist) (24, 25) not associated with a fall and were confirmed by local x-ray reports or by statements in the patients' records.

A patient satisfaction questionnaire was designed to reflect general feedback. In addition, spontaneously reported adverse events, including fractures, were recorded. Adverse events were reported at baseline and visits 4, 6, and 7.

Primary outcome

The primary outcome, persistence, was defined as the time in days from the date of the first dose of risedronate until discontinuation of treatment, assessed by electronic monitoring. Compliance was defined as the percentage of drug taken since first intake until discontinuation. Adherence was defined as the average daily percentage of patients who were both persistent (continued risedronate treatment) and compliant (took drug properly on that particular day).

Statistical analyses

The primary analysis was performed on the intention-to-treat (ITT) population, all patients who received at least one dose of risedronate and returned a functioning MEMS monitor. The safety population included all patients who received at least one dose of risedronate. Power calculations estimated that 13 patients within 166 centers, 2158 patients overall, were required to achieve a 90% power to detect a 10% improvement in adherence at 1 yr (assuming an intracluster correlation coefficient of 0.05). Adherence was plotted over time in both groups and compared between groups after reinforcement by means of a logistic regression which accounted for within cluster correlations.

Persistence was graphically presented as Kaplan-Meier survival curves. The effect of intervention on persistence was tested using an extension of the Cox-regression model that uses a robust covariance matrix to adjust for within-cluster correlations (26). If the hazard for discontinuation was not proportional over time, our preplanned analysis was to include reinforcement information in the model as a time-dependent covariate (26). Statistical comparisons were expressed in terms of discontinuation hazard ratios (HRs).

To assess potential factors associated with persistence, univariate analyses were performed on factors measured either at the cluster level (*e.g.* center size) or patient level (*e.g.* age, height, weight, body mass index, baseline BMD, compliance, comorbidities, presence of fracture, presence of risk factors, medication taken before or after breakfast, concomitant medication). Multiple regression analysis, using a stepwise variable selection procedure, was then performed on factors that reached statistical significance.

Treatment effect was examined by assessment of the incidence of new fragility fractures. Logistic regression analysis was used to compare vertebral fracture incidence and nonvertebral fracture incidence between groups. χ^2 test was used to evaluate the difference between groups in responses to the patient satisfaction questionnaire. For all analyses statistical significance was set at the 5% level.

Results

Patients

Disposition of patients is shown in Fig. 2. A total of 2382 patients from 171 different centers received risedronate and were included in the safety analysis. Of these, 2302 women (RE+, n = 1189; RE−, n = 1113) returned their electronic monitors and were included in the ITT population. In total, 39 patients (3.2%) from the RE+ group and 41 patients (3.6%) from the RE− group were excluded from the ITT analysis. Baseline characteristics are shown in Table 1 and were similar between groups. The average compliance with calcium and vitamin D intake during the study, based on pill counts, was 99% in each group and overall. Detail on the 209 patients who

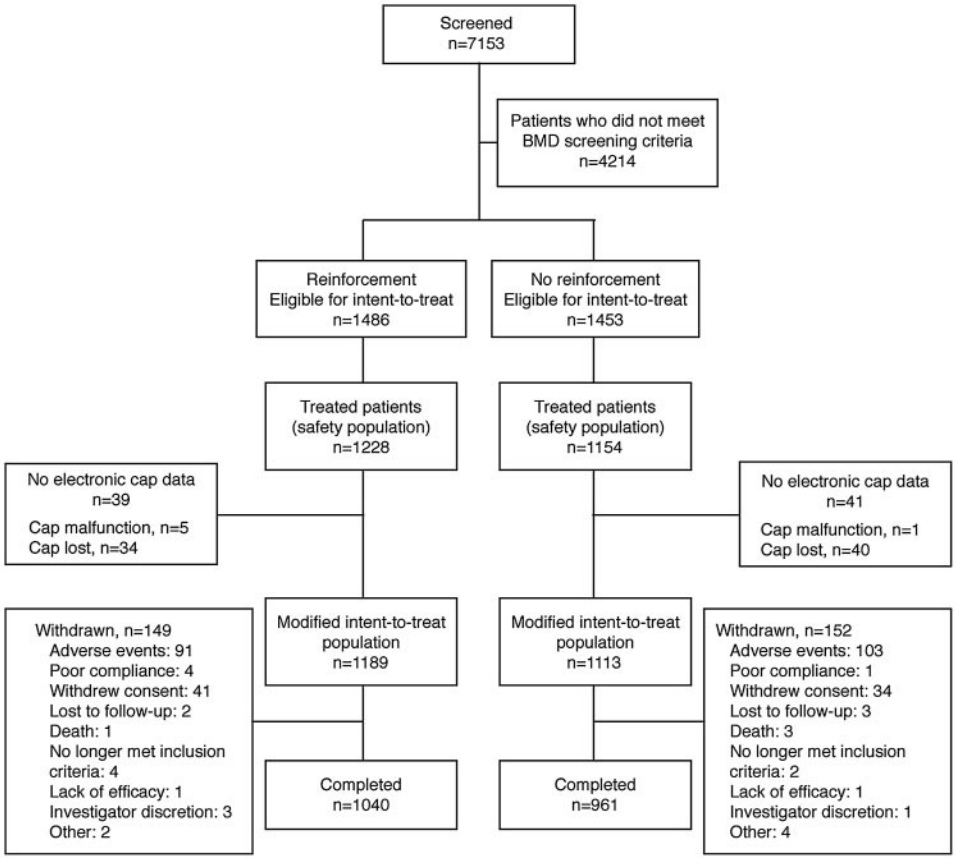

FIG. 2. Flow of patients through the study.

TABLE 1. Baseline characteristics of patients in the ITT analysis (n = 2302)

Characteristic	RE+	RE−
No. of patients	1189	1113
Mean age ± SD (yr)	71.1 ± 4.3	71.5 ± 4.5
Mean weight ± SD, range (kg)	64.1 ± 11.2	63.2 ± 10.7
Height (cm)	157.0 ± 7.0	157.4 ± 6.8
Mean spine T-score	−2.8 ± 1.0	−2.8 ± 1.0
Mean hip T-score	−2.0 ± 0.8	−2.0 ± 0.8
Patients with prevalent vertebral fracture [n (%)]	359 (30.2%)	330 (29.6%)
Patients with history of maternal hip fracture at older than 50 yr [n (%)]	133 (11.2%)	146 (13.1%)
Age when menses stopped, mean ± SD (yr)	47.7 ± 5.7	48.1 ± 5.7
Use of corticosteroids for longer than 3 months [n (%)]	40 (3.3%)	44 (4.0%)
Use of sex hormones [n (%)]	225 (18.9%)	204 (18.3%)
History of cigarette smoking [n (%)]	366 (30.8%)	351 (31.5%)
Alcohol use [n (%)]		
None	420 (35.3%)	372 (33.4%)
Less than three drinks per week	532 (44.7%)	485 (43.5%)
Three drinks or more per week	236 (19.8%)	255 (22.9%)

discontinued risedronate due to adverse events is provided in the *Safety analysis* section.

Patient adherence and persistence

Electronic monitoring of dosing histories demonstrated variation in adherence (compliance and persistence) between patients and within individual patient profiles. Samples of chronology plots from three patients with different degrees of adherence are shown in Fig. 3. After the first reinforcement visit, adherence was higher in the RE+ group, compared with the RE− group ($P = 0.01$). The difference in adherence between groups, although statistically significant, was marginal and is shown in Fig. 4. The large decrease in adherence over time is predominantly driven by the increasing number of patients who discontinue risedronate treatment (nonpersistence). Daily execution of the dosing regimen (compliance) among the patients who were still engaged with the treatment was very similar between both groups ($P = 0.8569$). Because maintaining long-term therapy is the most clinically relevant component of adherence with bisphosphonate treatment, persistence is the main focus of this manuscript.

Overall, persistence at 1 yr was high and was similar between groups (RE−, 77%; RE+, 80%; $P = 0.160$). As expected, the hazards for discontinuation were closely related to the type of reinforcement message and the HR between RE+ and RE− was not constant over time. After reinforcement, the message delivered in the RE+ group according to the uNTX response significantly ($P = 0.017$) affected the hazard of discontinuation. Compared with RE− patients, RE+ subjects who received a message based on more than 30% decrease in uNTX had a 29% reduction in the hazard of discontinuation [HR 0.71, 95% confidence interval (CI) 0.53–0.95; $P = 0.020$], indicating a significantly higher persistence with treatment. In contrast, RE+ patients who received a message based on a poor uNTX response were more than twice as likely to discontinue treatment, compared with the RE− group (HR 2.22, 95% CI, 1.27–3.89; $P = 0.005$). No differences in persistence were observed for RE+ patients who received a message based on a stable uNTX response, compared with the RE− group (HR 1.02, 95% CI, 0.74–1.40; $P = 0.920$). Of note, the numbers of visits with a good uNTX response (1369 visits) or a stable uNTX response (639 visits) were much higher than the number with a poor uNTX response (98 visits).

Because patients in the RE+ group could receive different messages at wk 13 and 25 (Table 2), an exact graphical representation of the time-varying model was not possible. Whereas the statistical analysis was performed using accurate time-varying information, a fair graphical approximation (Fig. 5) was achieved by classifying patients in the RE+ group into three categories: good response, more than 30% decrease in uNTX at both weeks; stable response, at least one stable uNTX response at either week and no significant increase in uNTX; and poor response, at least one uNTX increase more than 30% at either week.

Adjustment for compliance

Because compliance affects both persistence and uNTX outcomes, the observed effect of reinforcement could be caused by the information delivered to the RE+ patients or simply be a consequence of patient compliance. In the latter situation, compliance would be a confounding factor for the relationship between type of message delivered and persistence. To assess this, we compared the effect of uNTX on persistence between patients in the RE− group and patients in the RE+ group after adjusting for patient compliance. The results of this analysis showed that in the RE− group, there is no additional effect of uNTX results on persistence ($P = 0.7100$), whereas in the RE+ group, the uNTX results significantly affected persistence ($P = 0.0029$). These results confirm the causal effect of BTM feedback on patients' persistence to prescribed therapy.

Factors associated with persistence

A Cox multiple regression model was used to identify factors significantly associated with persistence. In addition to the effect of the type of feedback to RE+ subjects described above, a significant improvement in persistence was observed overall in patients who were more compliant with prescribed therapy. For example, a 10% increase in compliance (*i.e.* the proportion of prescribed drug taken since first drug intake until discontinuation) was associated with a 35%

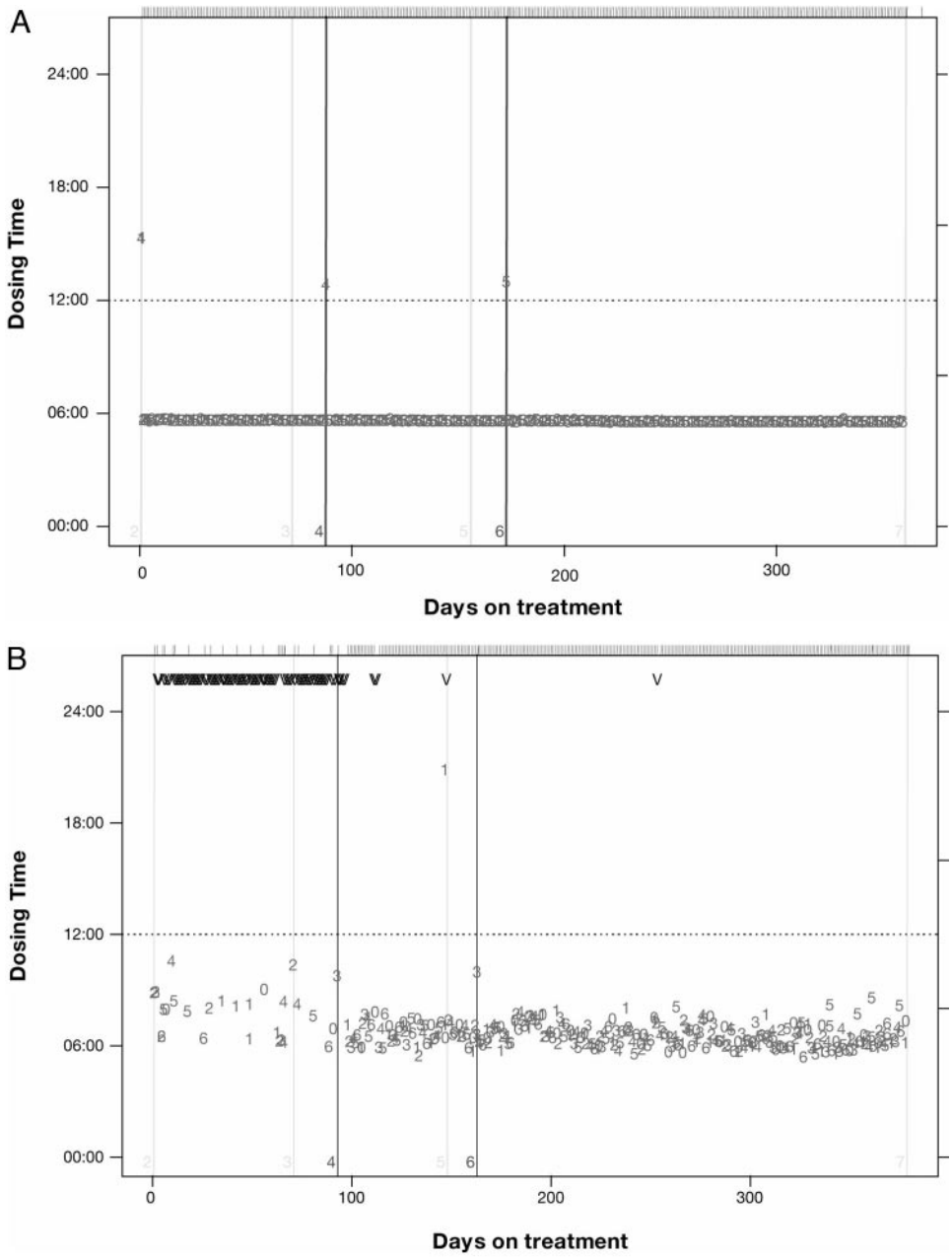

FIG. 3. Sample chronology reports for three patients. Days of the week are indicated by numbers: 0, Sunday; 1, Monday; 2, Tuesday; 3, Wednesday; 4, Thursday; 5, Friday; 6, Saturday. Days on which medication was not taken are indicated with a *v*. A, Data for a patient who took her medication consistently in the early morning throughout the study. B, Data for a patient who was noncompliant initially and improved after the first reinforcement visit.

decrease in the hazard of discontinuation (HR 0.65; 95% CI 0.62–0.68). Similarly, patients in both groups who elected to take study medication before breakfast were 24% less likely to discontinue (HR 0.76; 95% CI 0.60–0.95). In contrast, patients with ongoing morbidity had a 27% increase in the hazard of discontinuation for each five additional comorbidities (HR 1.27; 95% CI 1.07–1.49).

A significant interaction was observed between center size and reinforcement group. In the RE+ group only, the hazard of discontinuation decreased as the center size increased, *i.e.* large centers were more successful in delivering the reinforcement message than small ones. Regardless of center size, positive reinforcement decreased the hazard of discontinuation and thus increased persistence with prescribed therapy. After adjustment for all significant confounding factors (including center size), the type of feedback delivered to the patients in the RE+ group remained a significant factor associated with persistence.

Incidence of new vertebral and nonvertebral fractures

Baseline characteristics and presence of risk factors in the 1317 patients with spine x-rays at baseline and at 12 months (RE+ = 676; RE− = 641) were comparable with the ITT population (data not shown). Treatment was associated with a low incidence of new vertebral fractures (1.9%). In total, eight patients (1.2%) had nine new vertebral fractures in the RE+ group, compared with 17 patients (2.7%) with 18 new vertebral fractures in the RE− group (odds ratio 0.4; 95% CI 0.2–1.0). In the ITT population, the incidence of new non-

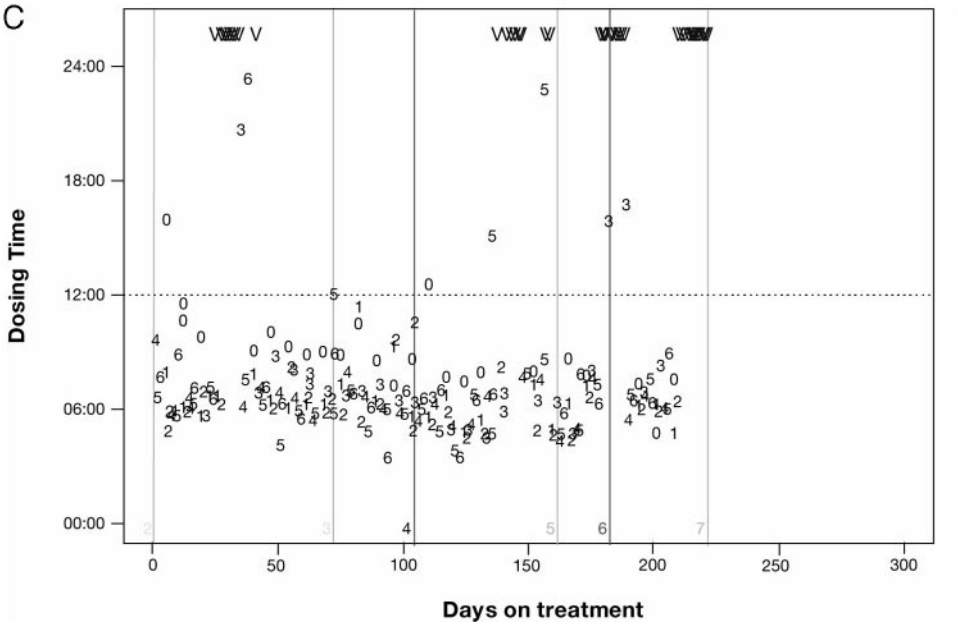

FIG. 3. *Continued.* C, Data for a patient who was mainly noncompliant throughout the study.

vertebral fractures at the six skeletal sites (clavicle, hip, humerus, leg, pelvis, and wrist) was also low (2.0%), including 22 fractures in RE+, compared with 24 in RE− (odds ratio 0.9; 95% CI 0.5–1.5). An additional 44 fractures occurred in ribs, toes, and fingers.

Patient satisfaction

Overall experience with risedronate was rated good to excellent in 92.4% of the RE+ group and 91.7% of the RE− group. For both groups, 84.6% were willing to continue taking risedronate for treatment of osteoporosis. Not surprisingly, 93% of the RE+ group reported they understood information they received well or extremely well, compared with 66.2% of the RE− women ($P < 0.0001$). This difference was also seen in the percentage of patients who reported the information they received was helpful or extremely helpful (RE+ = 93.0%, RE− = 63.4%; $P < 0.0001$).

Safety analysis

A total of 2382 patients were included in the safety analysis. Overall, 63% experienced an adverse event (AE) (1497 patients reported 3785 AEs); only 16% reported at least one event that was considered by the investigator to be related to the study treatment (389 patients reported 569 drug-related events). Upper gastrointestinal (GI) AEs were reported by 14% of patients (421 upper GI events reported by 337 patients). The most frequently reported upper GI AEs were dyspepsia (4%) and abdominal pain (4%). Most upper GI AEs were considered mild (66%) and no endoscopies were performed. The most frequently reported non-GI AEs (≥5%) were infection (6%), back pain (5%), and arthralgia (5%). Of the 209 patients (9%) who withdrew from the study due to treatment-emergent AEs, upper GI AEs were those most frequently cited (3%). A total of 93 clinical fractures were reported as AEs, 90 of which were nonvertebral.

Serious AEs (SAEs) were reported in 8% of patients (201 patients reported 245 SAEs), the most common of which was traumatic fracture (1%). The incidence of all other SAEs, including upper GI adverse events, was less than 1.0%. A total of 4% of SAEs (10 of 245) were considered possibly related to study medication. Five patients (0.2%) discontinued because of a drug-related SAE. Eight SAEs resulted in death, none of which were thought to be related to study treatment.

Discussion

The IMPACT study is the first prospective trial to assess the effect of providing BTM information on persistence with osteoporosis therapy, and the largest and longest trial to date that used objective electronic patient monitoring to assess persistence. Although persistence was not influenced by reinforcement overall, we found that the type of reinforcement message did influence treatment persistence. Although risedronate has been shown to reduce the risk of vertebral and nonvertebral fractures in postmenopausal women with osteoporosis (24, 25, 27), improving persistence or maintaining compliance to therapy in clinical practice is particularly important because osteoporosis is often asymptomatic but requires long-term medication.

Persistence with risedronate in this trial was higher than expected. Several factors may have contributed to this for both groups. Adherence tends to be higher in clinical trials than clinical practice (28–30). Furthermore, in our study, intensive patient follow-up occurred, even in the nonreinforced patients. Patient motivation may also have been higher than expected because all patients were aware that persistence was the primary outcome of the trial. Simple advice on how compliance can be improved, such as linking intake of medication to patient's habits like brushing teeth (31, 32), was also provided to investigators as part of the protocol. Regardless of these limitations, reinforcement remained a significant factor for persistence, albeit the overall increase was relatively small, compared with the nonrein-

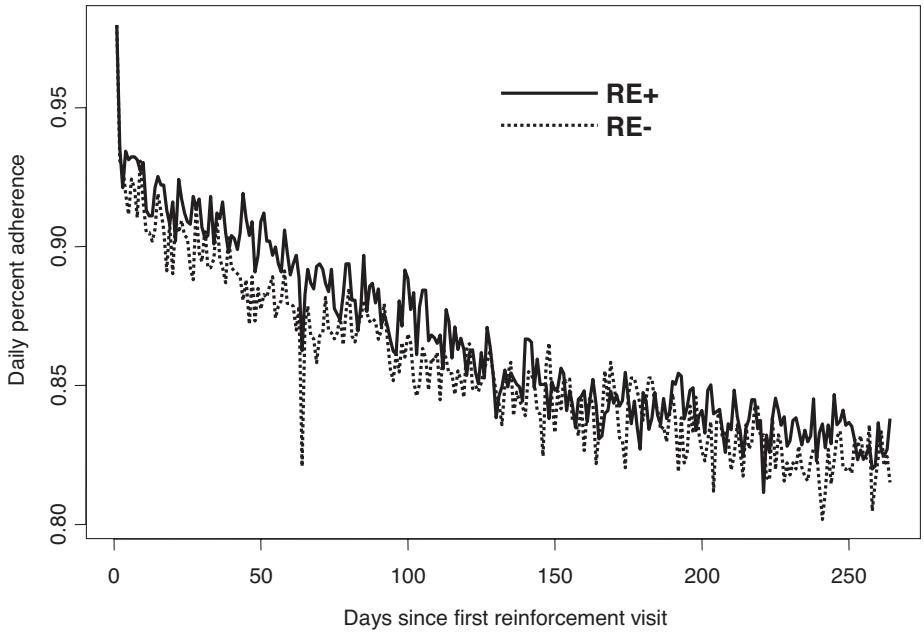

FIG. 4. Adherence (persistence and compliance) over time for both the RE+ (*solid line*) and RE− (*dotted line*) groups overall.

forcement group. We expect that an even larger effect of reinforcement would be seen in clinical practice.

These data also highlight the need for special attention to patients in whom uNTX increases above 30% from baseline. For the small percentage of patients in whom response to therapy was poor, providing this information became a major barrier for continuing the therapy. Thus, it is very important to develop new strategies to motivate these patients so that they continue treatment. They may require further assessment of compliance as well as an approach that would not call attention to their poor response.

Other factors that contributed to increased persistence in the RE+ group included medication intake before breakfast, performance of larger centers, and higher compliance with therapy. For example, patients taking a greater proportion of their medication at the beginning of the study were more likely to be persistent.

Based on findings in a subset of patients with complete radiographic measurements, reinforcement using BTM data was associated with a reduced risk of fracture. This may be explained in part by the significant increase in persistence in the patients within the RE+ group who received a reinforcement message based on 30% or greater decrease of uNTX (65% of visits). Although, overall, both RE+ and RE− groups were highly persistent with treatment, it is also possible that reinforcement may have positively affected patient behavior, translating into greater benefits in fracture reduction. This is supported by a greater understanding of the information received by the RE+ subjects which they also found more helpful. Whether monitoring osteoporosis treatment with BTMs will ultimately lead to better fracture outcomes requires further study aimed at this specific question.

Limitations of our study include the fact that the patients were highly motivated. This could explain why persistence was so high. Another limitation is the initiation of reinforcement at wk 13 rather than at baseline. Earlier reinforcement could decrease early drop-outs. Additional analyses were done on patients who did not discontinue treatment before they had the opportunity to receive a reinforcement message (visit 4), and the difference in persistence between the RE+ and RE− groups appeared larger in this subpopulation. Finally, we studied once-daily dosing, so the applicability to other dosing regimens is unknown. Further research repeated with once-weekly or once-monthly regimens, performed in a population closer to those seen in a general practice in osteoporotic patients, would be useful.

Studies in patients with chronic medical conditions have shown that combinations of more convenient care, information, counseling, reminders, self-monitoring, and family therapy are complex and not predictably effective (10, 33, 34). In postmenopausal women with osteopenia, nurse visits increased adherence to therapy, compared with no monitoring,

TABLE 2. Reinforcement messages based on type of BTM response delivered at wk 13 and 25 among patients in the RE+ group

Wk 13	Wk 25				Total
	No feedback[a]	Good	Stable	Poor	
No feedback[a]	109	4	7	4	124
Good	24	**511**	125	17	677
Stable	11	163	**145**	31	350
Poor	4	14	12	**8**	38
Total	148	692	289	60	1189

[a] Patients who discontinued study treatment.
The *numbers in bold* are those patients who had the same reinforcement message at both time points.

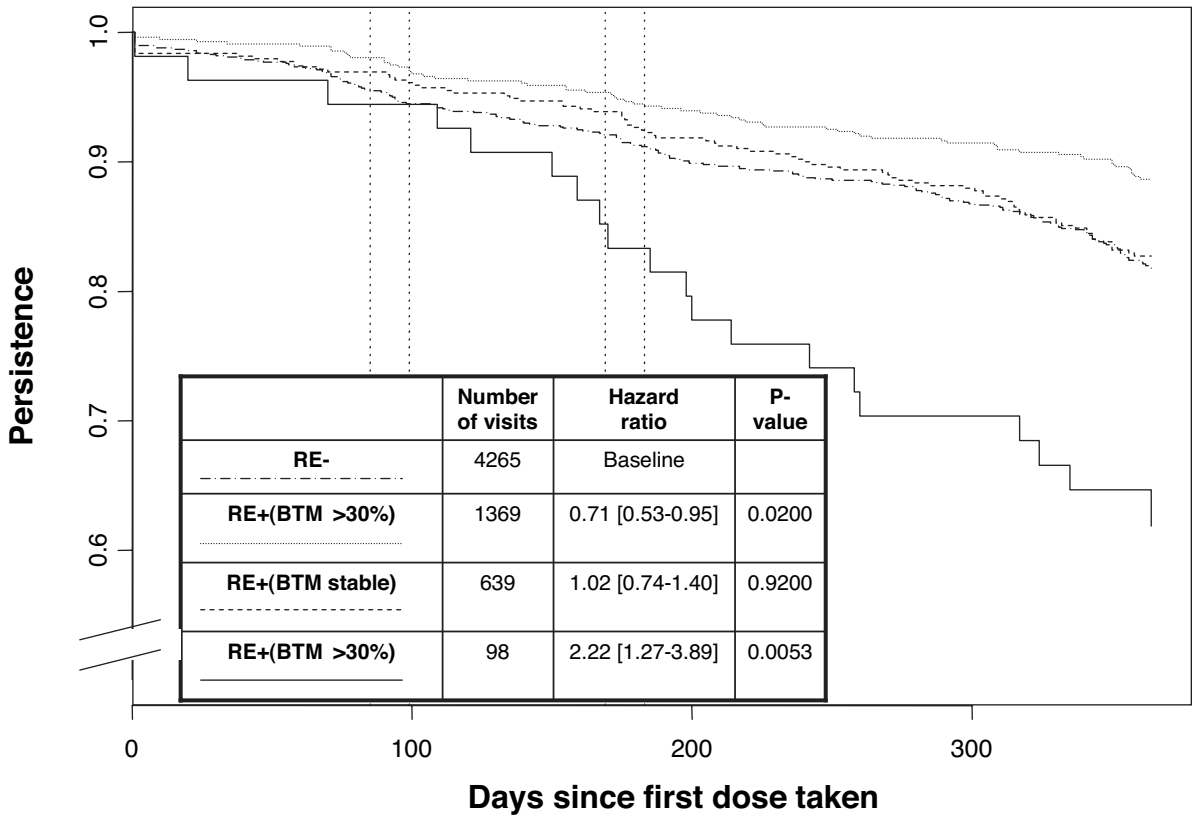

FIG. 5. Kaplan-Meier survival curves to show effect of feedback (uNTX) based on persistence (n = 2302). Because the reinforcement message delivered at wk 13 and 25 could be different for the same patient, graphical representation of the model was assessed by classifying the patients in RE+ into three message categories: good, more than 30% decrease from baseline in uNTX at wk 10 and 22; stable, at least one stable uNTX response at wk 10 or 22 and no increase in uNTX more than 30%; and poor, at least one uNTX increase more than 30% at wk 10 or 22. The numbers of visits corresponding to good uNTX response (1369 visits) or stable uNTX response (639 visits) were higher than those corresponding to a poor uNTX response (98 visits).

whereas nurse visits combined with marker measurements did not show any additional improvement over nurse visits alone (10).

In the present study, assessment of BTMs was useful for improving or maintaining persistence, depending on the patient's BTM response. Typically, treatment periods of 1–2 yr are necessary to show a measurable and reproducible BMD response to therapy (35); in contrast, early decreases in BTMs have been shown to predict subsequent reduction in fracture risk in osteoporotic patients and may therefore serve as a surrogate for early treatment response (18). However, routine use of BTMs has yet to be accepted and practical limitations, such as availability and reimbursement patterns across countries may limit their usefulness.

We conclude that feedback using BTM data provides a useful tool for patients who demonstrate a beneficial response to treatment, not only as a surrogate marker for efficacy but also to maintain and/or improve persistence with osteoporosis treatment. Monitoring BTMs in those patients with poor responses provides important information for the clinician to adjust strategies to ensure patients receive optimal treatment.

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