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IMPROVING ADHERENCE TO AND PERSISTENCE WITH ORAL THERAPY OF OSTEOPOROSIS.

Maria Luisa Bianchi, M.D., Piergiorgio Duca, M.D.1, Silvia Vai, M.D., Giuseppe Guglielmi, M.D.2, Raffaella

Viti, M.D.2, Claudia Battista, M.D.2, Alfredo Scillitani, M.D.2, Silvana Muscarella, M.D.2, Giovanni Luisetto,

M.D.3, Valentina Camozzi, M.D.3, Ranuccio Nuti, M.D.4, Carla Caffarelli, M.D.4, Stefano Gonnelli, M.D.4,

Carla Albanese, M.D.5, Viviana De Tullio, M.D.5, Giancarlo Isaia, M.D.6, Patrizia D'Amelio, M.D.6, Francesca

Broggi, Dr.Biol., Marina Croci, M.D.

Bone Metabolism Unit, Istituto Auxologico Italiano IRCCS, Milano; 1Unit of Biometrics and Medical Statistics, Department of Biomedical and Clinical Sciences, Ospedale Luigi Sacco, University of Milano, Milano; 2Casa Sollievo della Sofferenza IRCCS, S. Giovanni Rotondo, University of Foggia, Foggia; 3Department of Medicine, Division of Endocrinology, Bone Metabolic Diseases Service, University of Padova, Padova; 4Department of Internal Medicine, Endocrine-Metabolic Science and Biochemistry, University of Siena, Siena; 5Department of Radiological Science, Policlinico Umberto I, University La Sapienza, Roma; 6Department of Medical Science - Geriatrics and Metabolic Bone Diseases, University of Torino, Torino.

Corresponding author (address to which requests for reprints should be sent):

Maria Luisa Bianchi, M.D.

Bone Metabolism Unit

Istituto Auxologico Italiano IRCCS

Via L. Ariosto 13

20145 Milano, Italy

phone: +390261911-2505 or -2540

fax: +390261911-2519

e-mail: ml.bianchi@auxologico.it

ABSTRACT

Purpose: Osteoporosis affects millions of individuals worldwide. There are now several effective drugs, but adherence to and persistence with treatment are low. This 12-month multicenter, prospective, randomized study evaluated the efficacy of two different methods aimed at improving adherence and persistence through active patient involvement, compared with standard clinical practice.

Methods: 334 post-menopausal women, receiving an oral prescription for osteoporosis for the first time, were recruited and randomized into 3 groups: group 1 [controls, managed according to standard clinical practice]; groups 2 and 3 [managed with greater patient and caregiver involvement and special reinforcements: group 2, instructed to use several different “reminders”; group 3, same “reminders” as Group 2, plus regular phone calls from and meetings at the referring Center]. All enrolled women had two visits (baseline and 12 months).

Results: Of 334 enrolled women, 247 (74%) started the prescribed therapy. Of those who started, 219 (88.7%) persisted in therapy for at least 10 months. At final evaluation, only 114 women were considered as “fully adherent and persistent” (all doses taken throughout the 12 months). There were no significant differences regarding “full adherence” among the 3 randomized groups. Frequency of drug administration had a significant

influence: weekly administration had a >5-fold higher adherence and monthly administration an 8-fold higher adherence ($p < 0.0001$) than daily administration.

Conclusions: The special effort of devising and providing additional “reminders” did not prove effective.

Additional interventions during the follow-up, including costly interventions such as phone calls and educational meetings, did not provide significant advantages.

MINI-ABSTRACT

Osteoporosis treatment has low adherence and persistence. This study evaluated if active patient involvement could improve them. At 12 months, only 114 out of 344 participants were “fully adherent and persistent” (all drug doses taken throughout the study). Only frequency of drug administration had a significant influence on adherence.

KEYWORDS

adherence, persistence, osteoporosis, oral therapy, post-menopausal women

INTRODUCTION

Osteoporosis is a very common chronic disease. About 1,660,000 hip fractures occurred worldwide in 1990 and the forecast for 2050 is 6.26 million [1]. In the European Union (EU), in 2010, 22 million women and 5.6 million men were estimated to have osteoporosis. Three and a half million new fragility fractures were reported, of which 610,000 hip fractures (a 60% increase with respect to 380,000 hip fractures in 1996), 520,000 vertebral fractures, 560,000 forearm fractures and 1,800,000 other fractures. The economic burden of incident and prior fragility fractures was estimated at 37 billion euro. Incident fractures accounted for 66% of the total cost, fracture-related long-term care for 29% and pharmacological prevention for 5%. Previous and incident fractures accounted for the loss of 1,180,000 quality-adjusted life years. These costs are expected to increase by 25% in 2025 [2]. In Italy, there were 94,471 hip fractures in 2005, most of them due to osteoporosis, with 467 million euro of direct hospitalization costs and 531 million euro of rehabilitation costs [3]. Several effective drugs are currently available for the treatment of osteoporosis, and many double-blind randomized clinical trials have consistently demonstrated the efficacy of these drugs in reducing the risk of both peripheral and vertebral fractures [4,5].

Adherence to and persistence with therapy in chronic diseases have been addressed in several studies. Adherence (a term now preferred to "compliance") is the extent to which a prescribed drug regimen is followed by a patient. Persistence is for how long a patient continues taking a prescribed therapy without interruption. Both adherence and persistence are a challenge. In the USA, low adherence to treatment has been estimated to cause 33% to 69% of hospital admissions, with yearly costs of about 100 billion dollars [6]. In 2008, a systematic review considering 81 studies on the efficacy of specific interventions in improving adherence to treatment in chronic diseases (such as diabetes, asthma, hypertension and AIDS, but not osteoporosis), found that only 36 studies (44%)

reported positive effects with the proposed intervention, and that complex interventions were more effective [7].

Low adherence to therapy has been reported for osteoporosis [8]. Less than 70% of women with osteoporosis actually start the prescribed treatment; among those who start, about 50% discontinue it within 1 year; and among those who persist, only a minority fully respects the prescribed regimen (times and doses) [9,10]. In a study on 401 post-menopausal osteoporotic women prescribed daily oral alendronate, 13% did not even start therapy; and among those who started, 49% stopped taking it within 1 year and another 30% within 2 years [11].

The introduction of once-a-week (and, later, once-a-month) bisphosphonates, currently used by most patients, was expected to improve adherence, but subsequent evaluations still report sub-optimal adherence and persistence [12]. Most studies have reported that a high adherence to osteoporosis therapy is able to improve biochemical markers and bone mineral density (BMD) in the short-medium term, and a Canadian study found that the compliant women had a 16% lower fracture rate [10]. This result is very important as it demonstrates that also the long-term consequences of osteoporosis (fractures) could be significantly decreased if high adherence and persistence are achieved. Considering the social and economic burden of osteoporosis, improving adherence to and persistence with standard oral therapy could have a significant positive impact on both health and costs [13,14]. The published studies on the adherence to osteoporosis treatment have all evaluated the outcome of single interventions [15-18]. To our knowledge, this is the first randomized, prospective study designed to evaluate the changes in adherence to and persistence with treatment obtained with two different approaches, characterized by the increasing involvement of both patients and caregivers, compared with the simple, traditional "prescription and follow-up" method.

MATERIALS AND METHODS

Study Design

Multicenter, prospective, randomized study of women affected by primary osteoporosis, starting oral therapy.

Carried out at 6 Italian hospital Centers, distributed in Northern, Central and Southern Italy. Sixty women expected to be enrolled by each Center, with informed consent.

Actually, 334 women enrolled and randomized.

Inclusion Criteria

Women in menopause, aged 45-80 years, with a diagnosis of post-menopausal osteoporosis (with or without previous fragility fractures), receiving a prescription of an oral drug for osteoporosis for the first time.

Requirements: ability to read and understand simple educational materials and to answer simple questionnaires; availability for phone calls; ability to come to the hospital's outpatient clinic for meetings.

Exclusion Criteria

Women already on oral therapy for osteoporosis. Women with osteoporosis secondary to other diseases or affected by other diseases requiring complex drug therapy (e.g. cancer, renal insufficiency, uncontrolled hypertension, diabetes, etc.). Women with severe cognitive, visual or hearing impairment.

Definitions

Osteoporosis was defined as a T-score ≤ -2.5 at lumbar spine and/or hip (evaluated by dual X-ray absorptiometry [DXA]), according to the WHO criteria.

Study Outcomes

The study was aimed at evaluating the changes in adherence to therapy (*primary outcome*) and persistence with therapy (*secondary outcome*) for osteoporosis, obtained

with two different follow-up approaches, compared to the standard approach (simple medical prescription, periodic follow-up visits).

The study was approved by the Ethic Committees of all participating Centers. Design and conduction respected the Helsinki Declaration (revised version 2000), Good Clinical Practice guidelines, FDA regulations, and International Conference on Harmonization. The study was sponsored by the Agenzia Italiana del Farmaco (AIFA)

(<http://www.agenziafarmaco.gov.it>; AIFA protocol code: FARM53J37M). The Trial

Registration was:

EU Clinical Trials Register (EudraCT) (<https://www.clinicaltrialsregister.eu>) Number: 2007-000540-27

Enrollment

Starting on March 1, 2007, all the women consecutively visited for osteoporosis at each participating Center, if meeting the study criteria, were invited to participate in the study and to sign the informed consent. The study lasted longer than initially planned because a Center unexpectedly withdrew its participation and had to be replaced by another Center, that started enrollment on March 1, 2009. The first patient had her baseline visit on September 12, 2007. The last patient concluded the 12-month study on June 24, 2012.

Definitions

Adherence to treatment was rated as: high (>80% of prescribed doses actually taken), good (51-80%), poor (26-50%), or low (\leq 25%).

The patients were defined as “starting” or “not-starting” treatment, according to actual initiation of treatment.

The “starting” women were further divided in two subgroups: “persistent” with treatment (taking the drug for \geq 80% of time, i.e. \geq 10 out of 12 months, with a high or good

adherence, without interruptions for >2 weeks) and “not-persistent”. “Full adherence” was defined as taking all prescribed doses and “full persistence” as taking the prescribed drug throughout the 12 months of study.

Randomization

1. Group 1 (control group), managed according to standard clinical practice. At the baseline visit, these women were given their drug prescription, with the usual explanations and recommendations. A date for the next visit (after 12 months) was fixed.

2. Group 2, in addition, received the following materials:

- two booklets providing information on osteoporosis and the importance of adherence to treatment, written by the experts of an Italian patient association (“Lega Italiana Osteoporosi onlus”, <http://www.lios.it>), in collaboration with the Principal Investigator
- colored “memo” stickers for a calendar or diary
- a small alarm clock, easily programmable to ring at the time of daily, weekly or monthly drug doses;
- suggestions about the use of these “reminders” to improve adherence to therapy

3. Group 3, in addition to the same materials as Group 2, also received phone calls (every 3 months) to remind them to regularly take their therapy and to invite them to participate in patient meetings at their referring Center (4 meetings during the 12 months).

As an aid to check adherence, all patients received a diary to record each drug dose taken, and a plastic bag (bearing the project’s title and their personal study code) to keep all the used drug boxes and blisters (with start and end dates written on them). The diary and the filled bag were to be brought back to the referring Center at the final visit. The patients were instructed about the importance of providing accurate information, and that errors, oversights or other reasons for missing one or more doses would not have consequences or negative judgments. During the two visits (baseline and final), all patients

were administered a questionnaire, with questions focused on problems with drug-taking, dosage, clarity of directions, etc. Patients of Group 3 had also to fill in a questionnaire at the end of each meeting.

Visits

At both initial and final visits, the study's specially designed clinical record forms were used to record age, weight, height, presence of other diseases etc., bone DXA data (including T-scores), history of fractures (if any), prescribed therapy, changes during the year (if any), and the doctor's final estimate (interview-based) of the patient's adherence to therapy. If additional visits were required during the year because of special problems, the additional data were also recorded.

Doctors at the participating Centers were free to prescribe any of the several drugs available for oral treatment of post-menopausal and senile osteoporosis (bisphosphonates, SERMs, strontium ranelate). The study was not aimed at evaluating treatment efficacy, but only adherence and persistence, and their difference among the groups. The Coordinating Center did not interfere with the clinical decisions of the participating Centers.

Withdrawals and replacements

Considering the study aims, the only acceptable reason for withdrawal and replacement of an enrolled patient was physical impossibility to take any of the available oral therapies for osteoporosis (e.g. because of severe adverse reactions). All other reasons for withdrawal were considered as non-adherence/non-persistence.

Phone calls and group meetings (Group 3 only)

The Centers' doctors and nurses involved in telephone calls and patient meetings were trained by a psychologist to stimulate patient collaboration and to use specific indicators of adherence to treatment. Regarding the phone calls, a standard draft (with a predefined list of topics) was prepared. The date and time of all calls, including failed attempts, were recorded. Calls were considered "successful" only if the staff was actually able to contact the patient and discuss all relevant points with her.

The educational meetings were held on the participating Centers' premises. Only 4-6 patients at a time were invited, to facilitate interpersonal exchanges and active involvement. Patients' presence or absence was recorded. A predefined list of topics was used for the meetings to ensure homogeneity among the Centers.

Measurement of bone turnover markers

Three bone turnover markers were measured at baseline and 12-months, as an objective method to evaluate the actual adherence to treatment: two serum bone formation markers (bone-specific alkaline phosphatase [BSAP], osteocalcin [OC]) and one urinary bone resorption marker (N-terminal telopeptide of type 1 collagen [NTx]). Serum OC was measured by radioimmunological assay (RIA; DiaSorin, Italy); BSAP by immunoenzymatic assay (Quidel, USA); urinary NTx by enzyme-linked immunosorbent assay (EIA; Ostex Intern. Inc., USA).

All bone turnover markers were centrally measured by the Coordinating Center to avoid variability due to different laboratories and diagnostic kits. Blood samples were collected in the morning, after an overnight fast. For NTx, urine was collected during the preceding 24 hours.

Methods for assigning subjects to treatment groups

Randomization was performed centrally and designed to balance the sample size in the three groups and the distribution of patients among the different groups at each of the six Centers. Six separate randomization lists with 60 elements each were produced and kept at the Coordinating Center. Whenever a new patient was enrolled by a Center, the Coordinating Center provided the randomization group.

Outcome evaluation

Adherence to and persistence with treatment were evaluated with five different methods:

1. Doctors' judgment, based on the patient's interview at final visit
2. Analysis of questionnaires
3. Patient's diaries
4. Estimated amount of drugs taken, upon examination of the empty drug boxes and blisters collected by each patient in the study bag
5. Changes in bone turnover markers between baseline and final tests. The biological response to therapy was used as an objective measure of adherence, particularly for bisphosphonates. All biochemical measurements were performed blind to adherence data and randomization. In accordance with the literature, a change exceeding the least significant response (LSR) in individuals can be regarded as a statistically significant response. For multiple measurements, a statistically significant change is calculated as the ratio of LSR to the square root of the number of measurements. A "good response" was defined as a change >20%.

Methods 2-3-4 are indirect methods, based on the patient's carefulness, reliability, goodwill and good faith.

Cross-checking of the questionnaires, the empty boxes (with start and end dates) and the diaries was made to obtain a more reliable overall estimate of the drugs actually taken by

each patient during the year. Method 5 is an objective method used to check the patient's declarations. Moreover, for Group 3 patients, participation in the programmed educational meetings was considered a further indicator of adherence to treatment. BMD T-score change could not be used as an objective outcome because DXA is reimbursed by the Italian Health System at 18-month intervals only, and was thus not included at the final study visit.

Statistical Analysis

All data were collected by the Coordinating Center and analyzed in collaboration with a medical statistician (prof P. Duca). Statistical calculations were performed with SPSS 17.0 (SPSS Inc., Chicago, IL, USA). For the whole sample: descriptive statistics of socio-demographic, anamnestic and clinical characteristics (at baseline).

To test the significance of the observed differences: Student's t test for independent samples (2-tail test, $\alpha = 0.05$) for quantitative data; chi-square test or Fisher's exact test, calculating the odds ratio (OR) and the corresponding 95% CI, as appropriate. Chi square was calculated as 2 degrees of freedom. To compare the 3 groups: Anova one-way and logistic regression analysis, as appropriate.

RESULTS

Three-hundred thirty-four women were randomized into the three groups (Fig. 1). At baseline, the three groups showed no significant differences in the main variables (age, weight, height, age at menopause, spine and/or femoral BMD T-scores; data not shown). The distribution of women who did not even start therapy ("not-starting") among the three groups was significantly uneven (chi square $p=0.029$): the "not-starting" women were significantly more numerous in Group 1 (control group) and significantly less numerous in Group 3 (women who received the higher level of reinforcement) (Table 1). Overall, the "not-starting" women were 26% of the total, but this datum was heavily influenced by the high percentages observed in two centers (51,7% and 33,3% respectively). In the other four centers the "not-starting" women were 16,8% on average (36/214).

The "not-starting" women were, on average, 2 years older at baseline (95% CI: 0.1–3.8 years, $t=1.068$, $p=0.039$), and 4 years older at diagnosis of osteoporosis (95% CI: 1.4–5 years, $t=3.261$, $p=0.001$). Among women already using calcium and/or vitamin D supplements, the "starting" women were more numerous (OR=1.0, 95% CI: 1.1–4.0, $p=0.0164$). Considering hormone replacement therapy (HRT), of the 68 women who had been taking it in the past, 86.8% started osteoporosis treatment, vs. only 70.7% of those who did never take it (OR=2.7; 95% CI: 1.3–5.8; Fisher exact test $p=0.008$). With respect to previous known fractures, there was no statistically significant difference between the "starting" and the "not-starting" women. Regarding pain, 99 (72.8%) out of the 136 women reporting moderate to severe pain started treatment, vs. 148 (74.7%) out of the 198 women with no pain or mild pain (difference N.S.). Finally, no statistically significant differences were observed regarding starting or not starting therapy with respect to alcohol, coffee and tobacco use.

The distribution of "starting" vs. "not-starting" women was significantly related to frequency of drug administration (daily, weekly or monthly) (Table 2). The "starting" women were

84.7% of those prescribed a once-a-month drug, 65.4% of those prescribed a once-a-week drug, and 75.4% of those prescribed a once-a-day drug.

Overall, the "persistent" women (taking therapy for ≥ 10 months) were 88.7% of the "starting" women. Among the three randomization groups, there was no statistically significant difference in the percentage of women who did not persist in treatment, even if the percentage was unexpectedly (although not significantly) higher in Group 3 than in the other 2 groups (Table 3). Full persistence (taking therapy for 12 months) was observed in 215 women (87.0% of the "starting" and 98.2% of the "persistent" women).

There were no statistically significant differences between the "persistent" and the "not-persistent" women.

Persistence in treatment was observed in: 89% of the "starting" women who did not take any other drug, 90% of those already taking one drug, 85% of those already taking 2 or more drugs (chi square $p=0.644$); 89% of those taking calcium and/or vitamin D supplements, 88% of those not taking supplements (chi square $p=0.789$).

Among the "starting" women who had taken HRT, 89% were "persistent", vs. 91% of those who had never taken it (Fisher exact test $p=0.806$). Among the "starting" women without previous fractures, 90% were "persistent", vs. 87% of those with previous fractures (chi square $p=0.503$). Persistence was observed in 92% of the "starting" women without pain; 85% of those with thoracic-lumbar pain; 94% of those with pain at other sites (chi square $p=0.172$). Among the "starting" women, the "persistent" were 91.4% ($N=64$) of those prescribed a once-a-week drug, and 92.5% ($N=87$) of those prescribed a once-a-month drug, but only 81.9% ($N=68$) of those who had to take a daily drug (chi square $p=0.058$). Full adherence (all doses taken) and full persistence (12 months) were eventually observed in 114 women, i.e. 46.1% of the 247 "starting" women and 52% of the 219 "persistent" women. Full adherence was related to the frequency of administration but not to the type of follow-up (reinforcements) (Table 4). This is confirmed by logistic regression

analysis, whereby only the frequency of administration had a statistically significant influence on adherence. With respect to daily administration, there was a >5-fold increase in adherence with weekly administration, and an 8-fold increase with monthly administration ($p < 0.0001$): for weekly vs. daily treatment: OR=5.7, 95% CI: 2.7–11.8; for monthly vs. daily treatment: OR=8.0, 95% CI: 4.0–16.1. The other variables considered in the model (kyphosis, thoracic-lumbar pain, other therapies, previous fractures) did not show any statistically significant influence.

Adding-up the numbers of “not-starting”, “not-persistent” and “not-fully-adherent” women of the 3 groups, the results by intention-to-treat were not significantly different in the 3 groups (chi square $p = 0.297$).

At the end of the study, in the persistent women, the observed changes in bone turnover markers consistently reflected the expected effects of the drugs (Table 5): with bisphosphonates, a significant decrease in NTx, BSAP and OC markers; with strontium ranelate, a small increase in BSAP, no change in OC and a small decrease in NTx.

A high percentage of the “starting” women of all groups correctly completed the initial and final questionnaires:

71 out of 75 in Group 1 (94.7%), 77 out of 81 in Group 2 (95.1%) and 83 out of 91 in Group 3 (91.2%). Among the questions of “section A” (perceptions about therapy), only question #5 (“Do you think this therapy will modify your life habits?”) was associated with persistence in treatment. While 97% of women who answered “Not at all” persisted in treatment, only 88% of those answering “fairly much” or “much” did so (OR: 5.4; 95% CI: 1.7–17.5 $p = 0.004$). Among the questions of “section B” (sources of information on health and drugs) none was associated with persistence. In particular, regarding the “preferred” source of information, a high majority of women indicated their family doctor (58% exclusively, and 95% not exclusively). Even regarding the “main” source of information, 92% of the women indicated their doctor. There also was a highly significant difference in

persistence (84.8% vs. 95.9%; OR: 4.2; 95% CI: 1.5–12.1; Fisher exact test $p=0.009$) between the women saying they would not look for more information after enrollment (N=66) and those saying they would do so (N=147). Finally, considering the women with some previous knowledge about osteoporosis therapy: 100% of those (N=70) who had only heard about its benefits were “persistent”; vs. 89.3% (108 out of 121) of those who had also heard (or only heard) about its untoward effects (Fisher exact test $p=0.002$). Almost all the enrolled women (96%) considered the provided informative booklets useful. fewer women would have appreciated a telephone number to call (76%), an internet site (43%), or an e-mail address to write to (38%).

DISCUSSION

Adherence (formerly referred to as compliance) and persistence have been the object of many studies on osteoporosis therapy, mainly cross-sectional and retrospective. To our knowledge, this is the first prospective randomized study using different approaches to stimulate adherence to osteoporosis therapy.

Different studies from different countries consistently reported low adherence. For example, in the USA, 60 days after prescription of a bisphosphonate, 2,497 (29.5%) out of 8,454 women had not yet started taking the drug, and there was an association of older age and emergency department utilization with higher odds of non-adherence, and of prescription drugs and hospitalization with lower odds of non-adherence [19]. In a Canadian study on 11,249 osteoporotic women followed for 2 years, 51% were poorly compliant [10]. A study by Briesacher et al. [20] reported only modest variations in adherence to newly started drug therapies for six common diseases, including osteoporosis, strengthening the hypothesis that adherence is a general problem and not a disease- or drug-specific problem.

The importance of obtaining a high adherence to therapy is demonstrated by the lower fracture rates among bisphosphonate users with high adherence [10,13,14,21,22]. A recent review article analyzed the literature published between 1979 and 2009 regarding the magnitude of non-adherence among patients with osteoporosis, and the association between frequency and modality of drug administration with patient preference and adherence. The authors found that at 12 months, preference and adherence seemed to be higher with weekly than with daily bisphosphonates. The analyzed observational studies (6-12 months) reported discontinuation rates of 18–22% for daily and 7% for weekly bisphosphonates. Data on monthly bisphosphonates were conflicting and confounded by several variables (cost differences, patient support, definition of “persistence”).

Some studies suggested a preference for annual zoledronic acid infusions with respect to weekly bisphosphonates. Drug efficacy, side effects and route of administration seemed more important than frequency. Overall, adherence was difficult to quantify and might not be primarily influenced by frequency of drug administration [23].

The preferences regarding osteoporosis therapy were studied with a questionnaire in 1,150 Japanese patients: 60.3% preferred once-a-week drugs and 24% once-a-month drugs. If a doctor recommended a once-a-month drug, 32.5% would like to switch, 31.8% would be undecided, and 35.7% would prefer to continue with their current drug. The authors underline the importance of meeting the patient preferences if possible [24]. In a retrospective cohort study on 44,635 American women aged 50 years or more, 35.1% of patients on weekly alendronate, 32.5% of those on weekly risedronate, and 30.4% of those on once-a-month ibandronate were persistent (i.e. did not discontinue nor switch drugs during the 12-month study). Therapy was discontinued by 50% of patients after 109 days with alendronate, 95 days with risedronate, and 58 days with ibandronate ($p < 0.05$). While persistence was suboptimal with all treatments, patients receiving prescriptions for weekly alendronate were more likely to be persistent than those receiving the other drugs [25]. Carr et al found non-adherence to daily and weekly bisphosphonates to be independent of the decision to stop taking them (non-persistence).

Non-persistence was mainly associated with side effects, but also with other factors (dissatisfaction or concerns about therapy) that could be modified by the doctor through education, information, and concordant partnerships [26]. In a long-term study (up to 5 years of follow-up) on 8,610 Dutch patients initiating osteoporosis drugs (alendronate, risedronate, ibandronate, etidronate, raloxifene, strontium ranelate), persistence was 70.7%, 58.5%, 25.3% after 6 months, 1 year and 5 years, respectively. A higher risk of non-persistence within the first year was associated with once-a-day drugs, age < 60 years, and use of glucocorticoids [27]. A study by Curtis et al. on 2,748 osteoporotic

patients (mean age 62.0 years), compared adherence estimated by the doctor with that calculated from their patients' pharmacy claims. On average, doctors estimated that 67.2% of their patients were adherent, while only 40% proved to be actually adherent according to pharmacy data.

Such overestimation of adherence by physicians may negatively affect the doctors' ability to provide high quality care to osteoporosis patients [28].

Regarding our study, its strong points are its design (randomized prospective study using different approaches, with increasing efforts to involve patients), the homogeneity of the patient sample (inclusion and exclusion criteria), and – considering the lack of established methods to estimate adherence [18] – the four different methods devised to estimate adherence to and persistence with treatment, in addition to the doctors' subjective evaluation. The study has two main limitations. First, the presentation of the study to patients, as well as the additional procedures (including phone calls and meetings agendas) for Group 3, were identical for all the participating Centers, irrespective of specific local conditions. This might at least partly explain why two Centers had a particularly high number of low-adherence and low-persistence cases. Second, the length of the study (12 months) was probably too short to appreciate the different responses to therapy in function of adherence.

Overall, our study found “full adherence” (all doses taken) to treatment in only a minority of patients, 34.1% (114/334) of the whole sample, or 53% (114/215) of the fully-persistent women (drug taken for the whole period of 12 months). These results are only slightly better than the previously published reports that chronic patients take less than half of their prescribed therapies and often cease to take them after the first 6 months [29] and similar to a retrospective analysis of Taiwanese patients with osteoporotic vertebral or hip fractures, in which 38% of patients were compliant during the first year of treatment [22]. The study suggests that the higher attention given to patients of Groups 2 and 3 at

baseline (the time of prescription) and the availability of supportive tools did positively influence the decision to start therapy. This effect was particularly evident in group 3, where the number of starting women was clearly higher than in the above mentioned studies (82% vs. about 70%).

Factors positively associated with starting therapy were lower age at prescription (enrolment) and at diagnosis, previous HRT, frequency of administration of the prescribed drug. The identification of “persistent” and “not persistent” women was consistent with the observed changes in bone turnover markers, considering the type of drug used. Contrary to expectations, the different “reinforcements” utilized to support and actively involve patients did not influence persistence with therapy. Finally, responses to the final questionnaire showed that patients who considered their therapy “easy to follow” and those who reported “high adherence” were more likely to be persistent.

Regarding the main question of our study, it was somewhat surprising that the special effort of devising and providing “reinforcements” of adherence to therapy did not prove effective. Quite unexpectedly, there were no significant differences in full adherence in the 3 groups. In particular, Group 3, who received the highest level of attention and resources, did not show any better adherence than the other two. Special measures during the follow-up, in particular costly measures like reminder phone calls and educational meetings for small groups of patients, did not provide additional advantages. Only frequency of drug administration strongly influenced adherence.

While the statistical analysis of our results does not allow more positive conclusions, on the basis of the responses to questionnaires we still believe that providing factual and clear information about the goals and importance of osteoporosis therapy is highly valuable and might possibly improve adherence in the long-term by increasing awareness of the disease and its complications (fragility fractures) in the community. Free, widely available, and easily-written educational leaflets and booklets might prove cost-benefit

effective, as well as – at least for younger patients – reliable information made available via internet. Reminding “stickers” and diaries were also appreciated by many patients. More sophisticated and costly “reinforcements” or memory-aids – like programmable clocks, alarm pill boxes and the like – or even direct phone or email contacts initiated by the caregivers, although useful in some cases, cannot be considered, at least for the moment, as cost-effective in improving adherence to therapy of osteoporosis.

Most studies on osteoporosis and compliance/adherence concluded that the specificity of the disease may have a relevant influence on adherence to and persistence with therapy [8]. In our opinion, the main reasons are: first, before the occurrence of fractures, osteoporosis does not cause pain or other symptoms, so the patient is highly likely to underestimate its severity; and, second, the patient is unable to immediately appreciate the positive effects of therapy as they cannot be directly perceived (as would happen, for example, with chronic pain, diabetes, hypertension, etc.) but can only be revealed by specific exams (bone densitometry), performed at long intervals (12-18 months).

Moreover, the adherence to and persistence with treatment may depend on the actual coverage of osteoporosis treatment by the different National Health Systems: for example, the Italian system only provides limited coverage for the treatment of uncomplicated osteoporosis.

The available data suggest that to adhere to and persist with prescriptions for fracture prevention, patients must be convinced of being at significant risk of fractures, that the prescribed therapy is not only effective but also safe and devoid of long-term harm, that there are no equally effective alternative (non-medicinal) therapies, and that therapy will not significantly change their living habits or affect daily tasks [30].

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Conflicts of interest

The authors Maria Luisa Bianchi, Piergiorgio Duca, Silvia Vai, Giuseppe Guglielmi, Raffaella Viti, Claudia

Battista, Silvana Muscarella, Giovanni Luisetto, Valentina Camozzi, Ranuccio Nuti, Carla Caffarelli, Stefano

Gonnelli, Carla Albanese, Viviana De Tullio, Giancarlo Isaia, Patrizia D'Amelio, Francesca Broggi, Marina

Croci declare that they have no conflict of interest.

Authors' contributions

Maria Luisa Bianchi conceived and designed the trial protocol and submitted it to AIFA; had full access to all the study data; wrote the first draft and final version of the article.

Piergiorgio Duca performed the randomization procedure and statistical analysis.

Francesca Broggi performed all the centralized lab tests.

Silvia Vai collaborated in the study coordination and data management.

Marina Croci assisted for the educational and psychological aspects of the protocol.

All authors participated in the enrolment and follow-up of patients, discussed the results, and commented the drafts and the final version of the article.

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List of Abbreviations

AIDS Acquired Immuno-deficiency Syndrome

BMD Bone mineral density

CI Confidence interval

DXA Dual X-ray absorptiometry

EU European Union

FDA Food and Drug Administration

HRT Hormone replacement therapy

LSR Least significant response

NTx N-terminal telopeptide of type 1 collagen

OC Osteocalcin

OR Odds ratio

SERM Selective estrogen receptor modulators

WHO World Health Organization

FIG. 1 Flow-chart of enrolment and different phases of the study

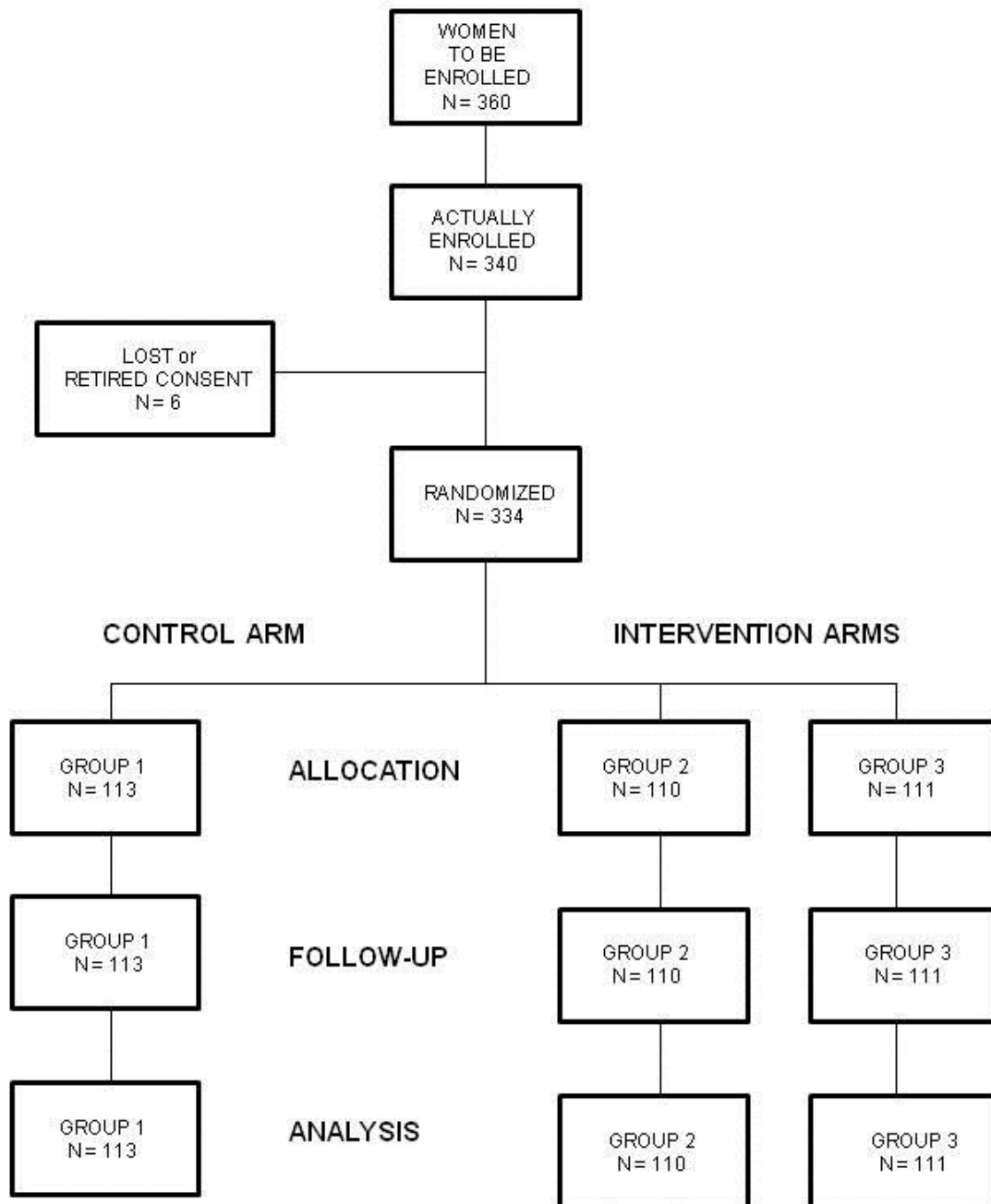


TABLE 1: DISTRIBUTION OF WOMEN STARTING OR NOT-STARTING TREATMENT ACCORDING TO RANDOMIZATION

GROUP

	GROUP 1 No. = 113	GROUP 2 No. = 110	GROUP 3 No. = 111	TOTAL No. = 334
NOT-STARTING	38 (33.6%)	29 (26.4%)	20 (18.0%)	87 (26.0%)
STARTING	75 (66.4%)	81 (73.6%)	91 (82.0%)	247 (74.0%)

The frequency of not-starting vs. starting women was significantly different in the 3 groups (CHI square 2 DoF p =0.029)

In Group 1 (i.e the control group, women who received the prescription without any reinforcement), the “not-starting” were significantly more than in Group 3 (women who receive the higher level of reinforcement).

DoF = degrees of freedom

**TABLE 2: DISTRIBUTION BETWEEN STARTING AND NOT-STARTING WOMEN
ACCORDING TO FREQUENCY OF
DRUG ADMINISTRATION**

	STARTING		No. of women
DRUG ADMINISTRATION	NO No. of women	YES No. of women	TOTAL
DAILY	27	83	110
WEEKLY	37	70	107
MONTHLY	17	94	111
TOTAL No. of WOMEN	81*	247	328

CHI

square

2 DoF $p = 0.00435$

DoF = degrees of freedom

* Data about the drug prescribed to 6 “not-starting” women are missing.

TABLE 3: THE “STARTING” WOMEN: DISTRIBUTION OF PERSISTENT vs. NOT-PERSISTENT WOMEN ACCORDING TO RANDOMIZATION GROUP

	GROUP 1 No. = 75	GROUP 2 No. = 81	GROUP 3 No. = 91	TOTAL No. = 247
PERSISTENT	69 (92.0%)	73 (90.1%)	77 (84.6%)	219 (88.7%)
NOT-PERSISTENT	6 (8.0%)	8 (9.9%)	14 (15.4%)	28 (11.3%)

Difference not significant in the 3 groups (CHI square 2 DoF p =0.288).

DoF = degrees of freedom

TABLE 4: THE 114 FULLY ADHERENT WOMEN (i.e. “PERSISTENT WHO NEVER MISSED A DOSE”): DISTRIBUTION

ACCORDING TO RANDOMIZATION GROUP

GROUP	DRUG ADMINISTRATION (No. of women)			TOTAL (No. of women)
	<i>DAILY</i>	<i>WEEKLY</i>	<i>MONTHLY</i>	
1	5/23 = 22%	11/19 = 58%	21/33 = 64%	37/75 = 49%
2	3/26 = 11%	16/27 = 59%	14/28 = 50%	33/81 = 41%
3	7/34 = 21%	12/24 = 50%	25/33 = 76%	44/91 = 48%
TOTAL	15/83 = 18%	39/70 = 56%	60/94 = 64%	114/247 = 56%

TABLE 5: BONE TURNOVER MARKERS: OBSERVED CHANGES AT 12-MONTHS VS. BASELINE

	TREATMENT	NOT-PERSISTENT	PERSISTENT	p	L 95% CI	U 95% CI
serum BSAP (ng/ml)	1	5.44 (6.35) 12	12.82 (9.72) 143	<0.00001	6.9	7.8
	2	6.48 (5.38) 14	4.09 (9.45) 67	<0.00001	-3.0	-1.8
serum OC (ng/ml)	1	2.08 (12.64) 12	8.42 (9.72) 147	<0.00001	5.9	6.8
	2	3.64 (10.88) 14	3.12 (11.72) 67	0.1784	-1.3	0.23
urinary NTx (nMBCE/mMCR)	1	23.2 (36.03) 12	42.32 (33.98) 145	<0.00001	17.5	20.7
	2	7.0 (63.81) 14	12.82 (36.04) 66	<0.00001	3.1	8.6

BSAP = bone specific alkaline phosphatase; OC = osteocalcin; NTx = N-terminal telopeptide of collagen type 1

Treatment 1 = bisphosphonates (taken daily, weekly or monthly)

Treatment 2 = strontium ranelate (taken daily)