Alendronate soluble solution: a higher adherence rate in the treatment of osteoporosis

Stefano Coaccioli[1]
Giorgio Celi[1]
Mariano Edoardo Crapa[1]
Francesco Masia[1]
Maria Luisa Brandi[2]

[1] General Medical Clinic and Medical Therapy, Rheumatology and Medical Therapy of the Pain, University of Perugia, "Polo di Terni", "AO Santa Maria" of Terni, Terni, Italy
[2] Diseases of the Mineral and Bone Metabolism, Department of Medicine, University of Firenze, "Policlinico Careggi", Firenze, Italy

Address for correspondence:
Stefano Coaccioli, MD, PhD
General Medical Clinic and Medical Therapy
University of Perugia, "Polo di Terni"
"AO Santa Maria" of Terni
Via T. di Joannuccio 1
05100 Terni (TR), Italy
Phone: +39 0744205365
E-mail: stefano.coaccioli@unipg.it

Summary

***Introduction*. Since low adherence to a long-term therapy results in a poor clinical outcome and significantly increases healthcare costs, adherence to the treatment of chronic disorders is an issue of great interest. This is particularly true of the treatment of osteoporosis (OP).**
***Purpose of study*. Adherence to the osteoporosis therapy in patients treated with bisphosphonates in tablet form has been evaluated in comparison with the adherence of those taking alendronate in soluble solution.**
***Methods and materials*. Here we present a retrospective study of 245 patients treated with alendronate, risedronate and ibandronate tablets and a prospective study of 118 patients treated with soluble alendronate. In both studies, patients have been observed for a period of 12 months.**
***Results*. The analysis of patients' persistence with the treatment plan, assessed at three, six and 12 months, revealed a significantly higher adherence ($p < 0.005$) in the cohort of patients treated with soluble alendronate (92.37% at 12 months) compared with those who followed the course of treatment with tablets (65.4 %, 12 months).**
***Conclusions*. The investigation showed higher adherence to the oral therapy with soluble alendronate, demonstrating that a formulation obtained by this method can contribute to a higher level of persistence with the treatment of a disease such as osteoporosis, which requires a long-term therapeutic plan.**

KEY WORDS: adherence; soluble alendronate; bisphosphonate; compliance; osteoporosis.

Introduction

The adherence to a therapeutic plan, especially in the treatment of a chronic disease or a necessarily prolonged therapy, constitutes one of the fundamental objectives in clinical practice (1, 2).
In this context, osteoporosis represents an emblematic case in which the only pharmacological approach capable of reducing the risk of fracture necessitates adherence to therapy, which must cover a suitable period of time and which, above all, should never be suspended in any arbitrary way (3).
Numerous studies have tackled the problem of adherence to bisphosphonate therapy, as reported below. A detailed review conducted in Spain showed low adherence to treatment with bisphosphonates, with a persistence average of six months, resulting in an increased risk of fracture, especially vertebral fracture (4). A retrospective cohort study conducted in Germany showed that the average duration of the treatment with oral bisphosphonates was 145 days. The persistence after one year was 28%, with no significant differences between the patients receiving the weekly treatment and those receiving the monthly treatment, while the persistence with daily doses at one year was only 7.2%. The adherence to treatment with bisphosphonates was the only factor that significantly decreased the risk of fracture (5). A Dutch study conducted on postmenopausal women with OP found that after one year, 51.9% of the subjects who used alendronate weekly had continued the therapy, while for those who undertook a daily therapy with different types of bisphosphonates (alendronate, risedronate, etidronate) the persistence was significantly lower after one year, at between 30.1 to 42.2%. The incidence of gastrointestinal side effects was also associated with lower therapy persistence (6). An American investigation has examined the factors associated with premature discontinuation of oral bisphosphonates treatment, defined as the discontinuation of therapy within 60 days of the prescription being issued. It was observed that 30% of women suspended the therapy within 60 days of the issuing of the prescription, mainly the oldest and those who had started their treatment in an emergency unit. The therapies prescribed by internists and rheumatologists were associated with a lower risk of premature discontinuation compared with those prescribed in primary health care centres (7).
A study conducted in France analysed data from the prescriptions database (TALES) relating to women over 45 years of age who had received their first monthly prescription of ibandronate or weekly prescription of bisphosphonates in 2007. Their therapy persistence was evaluated as follows. The persistence at 12 months was 47.5% for monthly ibandronate and 30.4% for weekly bisphosphonates; by eliminating some potentially confusing variables, it was found that

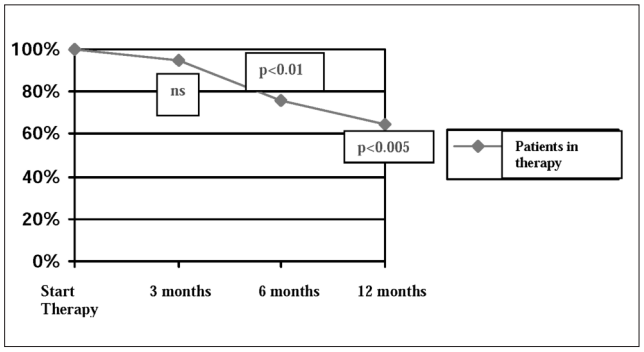

Figure 1 - Therapy persistence for patients (245) treated with bisphosphonates in tablet form.

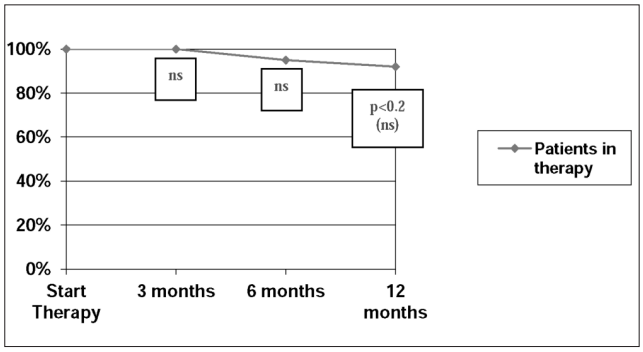

Figure 2 - Therapy persistence for patients (118) treated with soluble alendronate.

women receiving monthly therapy had a 37% lower chance of abandoning the therapy compared with those receiving a weekly treatment (8). A Canadian study involving over 450,000 subjects with an average age of 75 has showed a rate of continuation with oral bisphosphonate therapy of 63% at one year and 46% at two years (9). An American study compared the adherence to and persistence with daily and weekly treatment with bisphosphonates. The women who took bisphosphonates weekly had significantly higher adherence than those who received a daily therapy (69.2 *vs* 57.6%). Even the persistence at one year was significantly higher in those women who had received a weekly treatment (44.2 *vs* 31.7%) (10). A prospective study conducted in France of a cohort of women treated with different antiosteoporotic oral drugs, including bisphosphonates therapy administered monthly, weekly and daily, showed that the persistence at one year was 50% in women given a monthly treatment, 37% in women receiving a weekly treatment and 10% in women receiving a daily therapy (11). A survey conducted in Bulgaria has found high persistence rates for those patients who took alendronate once a week and ibandronate once a month. The persistence at 12 months was 86.8% and 58.94% at 24 months (12). An authoritative retrospective German study assessed the persistence of therapy with different antiosteoporotic drugs. At 12 months, the persistence of the therapy with different bisphosphonates (zoledronate, ibandronate, alendronate, etidronate or risedronate) was between 17.3 and 65.6%, with a higher persistence in those subjects who had received bisphosphonates intravenously (13). In order to evaluate the adherence to the osteoporosis therapy with bisphosphonates, we present here a retrospective study of patients treated with alendronate, risedronate and ibandronate tablets, as well as a prospective study of patients treated with soluble alendronate. In both studies, patients were followed for a period of 12 months. The study was conducted for the purpose of evaluating the persistence of the treatment with bisphosphonates in patients affected by osteoporosis, comparing subjects treated with alendronate in liquid form with other patients treated with bisphosphonates in tablet form.

Methods and materials

Our investigation has observed a total of 363 patients (288 women and 75 men) and it has been conducted through a retrospective and a prospective study. All patients took calcium and vitamin D supplements in conformity with accepted standards.

The **retrospective study** involved 245 patients (187 women: average age 61.8, range 46-71; 58 men: average age 72.4, range 68-77) taking bisphosphonate tablets (alendronate [35mg a week, 70mg/two days a month: 104 patients]; risedronate [35mg a week: 95 patients]; ibandronate [150mg a month: 46 patients]). The **prospective study** involved 118 patients taking alendronate through a soluble solution (Bonasol; Bruno Farmaceutici SpA, Rome) at a dose of 70mg a week (101 women: average age 63.2, range 47-69; 17 men: average age 70.7, range 65-80).

The subjects who took bisphosphonates in tablet form for more than a year were contacted by telephone and interviewed in order to find out further information concerning their therapy adherence. They were asked whether or not the treatment had been stopped and, if so, how long after the beginning of their treatment it was stopped. The subjects taking soluble alendronate were contacted by telephone at three, six and 12 months after the beginning of their therapy and were asked if they had stopped their treatment.

In respect of statistical evaluation and the expression of significance, we used the Student's t-test as the test for paired data in the two studies and as the test for unpaired data in comparisons between the studies. Further confirmation of the statistical comparison between the two groups was made through the use of the χ^2 test.

Results

Retrospective study. Of the 245 patients taking bisphosphonate tablets, 12 (4.89%) had discontinued the treatment three months after the beginning of their therapy (p=n.s.). Of the 233 remaining subjects, 58 (23.67% of the initial number) had discontinued their therapy after six months (p<0.01). Twelve months after the beginning of the therapy, 85 patients (34.6% of the total number) had discontinued their treatment (p<0.005). Therefore, 160 patients remained undergoing therapy (65.4% of the total number). There were no significant differences in the three groups between the patients taking the three different kinds of bisphosphonates in tablet form and those with other administration regimes (Figure 1).

Prospective study. Of the 118 patients taking soluble alendronate, none had discontinued the therapy after three months since the beginning of their treatment. After six months, six patients (5.08%) had discontinued their therapy (p=n.s.). After 12 months, the therapy had been discontinued by nine subjects (7.63% of the initial number). Therefore, 109 subjects remained undergoing therapy (92.37% of all patients) (p<0.2=n.s.) (Figure 2).

Conclusions

The low adherence to the treatment of a chronic disorder is a widespread problem; indeed, it has been shown that about 50% of patients do not follow the scheduled therapeutic treatment plan (1, 2, 14, 15). This has two major consequences, represented by a reduced therapeutic effect and an increase in healthcare costs (1-3). The improvement of therapy adherence, especially in cases of long-term therapy, ensures far greater safety for the patients in question; therefore, all interventions aiming at improving adherence had an important impact, far greater than the impact of any other therapeutic approach on all treated individuals (14, 15).

In developed countries, as mentioned, the rate of adherence to long-term treatments often falls to 50%: in the U.S., only 51% of hypertensive patients adhere to their treatment (16, 17); a similar situation holds for antidepressant therapy (18) (adherence varies between 40 and 70%), while in Australia only 43% of patients take medication according to their prescription. In summary, a non-optimal clinical outcome may occur in conjunction with poor adherence to the treatment plan (19).

More precisely, adherence is considered to be the extent to which the behaviour of a given patient matches all medical recommendations with agreed actions (20). Adherence cannot be simply equated with compliance (21), in which the patient's role is essentially passive (WHO Adherence Meeting 2001 definition: the extent to which the patient follows medical instructions); by contrast, adherence considers the patient in an active role (WHO Adherence Meeting 2003 definition: the extent to which the behaviour of a patient following a drug therapy corresponds to the directions agreed with the doctor). However, there are many factors which influence the adherence to therapy: the method of administration, the influence of the patient's lifestyle, the number of administrations in a given time (21) and, in the final analysis, probably the intrinsic characteristics of the medicinal product itself (tablets *vs* drinkable solution).

It has now been widely demonstrated that in osteoporosis therapy, adherence to therapy represents a fundamental factor able to significantly reduce the risk of fractures (1-3). As explained in our introduction, the global rate of adherence to the treatment is between 30 and 70% (14-16). Even our retrospective study, conducted on 245 patients with osteoporosis, who were monitored for 12 consecutive months and whose therapy took the form of the administration of bisphosphonates (alendronate, risedronate and ibandronate) in tablet form, has shown that about 5% of patients had discontinued the treatment within three months, 23% within six months and that almost 35% had abandoned the therapy after 12 months of observation. The availability of a soluble alendronate with a pleasant mouthfeel and a pleasant taste motivated us to perform a prospective 12 month observation of 188 patients who had been advised to take oral soluble alendronate in vials. None of the patients had discontinued their therapy after three months, 5% had discontinued their therapy within six months and only about 8% of the patients had discontinued it in the following 12 months: in other words, one year on from the beginning of their soluble alendronate therapy, over 90% of patients continued to adhere to the agreed treatment plan.

In the light of our investigations, we can observe that the persistence of osteoporosis therapy with soluble alendronate is significantly higher than that observed in most studies available in contemporary medical literature in which patients received an oral therapy in tablet form.

References

1. Osterberg L, Blaschke T. Adherence to Medication. NEJM. 2005;353 (5):487-97.
2. Haynes RB, et al. Interventions for helping patients to follow prescriptions for medications. Cochrane Database for Systematic Reviews. 2001;1.
3. Dunbar-Jacob J, Mortimer-Stephens MK. Treatment Adherence in Chronic Diseases. J Clin Epidemiol. 2001;54(suppl.1):S57-60.
4. Imaz I, Zegarra P, Gonzàlez-Enrìquez J, Rubio B, Alcazar R, Amate JM. Poor bisphosphonate adherence for treatment of osteoporosis increases fracture risk: systematic review and meta-analysis. Osteoporos Int. 2010;21(11):1943-51.
5. Hadji P , Claus V, Ziller V, Intorcia M, Kostev K, Steinle T. GRAND: the german retrospective cohort analysis on compliance and persistence and the associated risk of fractures in osteoporotic women treated with oral bisphosphonates. Osteoporos Int. 2012;23(1):223-31.
6. Penning-van Beest FJ, Goettsch WG, Erkens JA, Herings RM. Determinants of persistence with bisphosphonates: a study in women with postmenopausal osteoporosis. Clin Ther. 2006;28(2):236-42.
7. Reynolds K, Muntner P, Cheetham TC, Harrison TN, Morisky DE, Silverman S, Gold DT, Vansomphone SS, Wei R, O'Malley CD. Primary non-adherence to bisphosphonates in an integrated healthcare setting. Osteoporos Int. 2013;24(9):2509-17.
8. Cotté FE, Fardellone P, Mercier F, Gaudin AF, Roux C. Adherence to monthly and weekly oral bisphosphonates in women with osteoporosis. Osteoporos Int. 2010;21(1):145-55.
9. Burden AM, Paterson JM, Solomon DH, Mamdani M, Juurlink DN, Cadarette SM. Bisphosphonate prescribing, persistence and cumulative exposure in Ontario, Canada. Osteoporos Int. 2012;23(3):1075-82.
10. Cramer JA, Amonkar MM, Hebborn A, Altman R. Compliance and persistence with bisphosphonates dosing regimens among women with postmenopausal osteoporosis. Curr Med Res Opin. 2005;21(9):1453-60.
11. Confavreux CB, Canoui-Poitrine F, Schott AM, Ambrosi V, Tainturier V, Chapurlat RD. Persistence at 1 year of oral antiosteoporotic drugs: a prospective study in a comprehensive health insurance database. Eur J Endocrinol. 2012;166(4):735-41.
12. Kuzmanova SI, Solakov PC, Geneva-Popova MG. Adherence to bisphosphonate therapy in postmenopausal osteoporotic women. Folia Med (Plovdiv). 2011;53(3):25-31.
13. Ziller V, Kostev K, Kyvernitakis I, Boeckhoff J, Hadji P. Persistence and compliance of medications used in the treatment of osteoporosis-analysis using a large scale, representative, longitudinal German database. Int J Clin Pharmacol Ther. 2012;50(5):315-322.
14. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence (Review). The Cochrane Collaboration 2008.
15. WHO. Adherence to long-term therapies. Evidence for action. 2003.
16. Evans CE. Compliance with antihypertensive medication. Can Fam Physician. 1985;31:335-40.
17. Cramer JA. Consequences of intermittent treatment for hypertension: the case for medication compliance and persistence. Am J Man Care. 1998;4(11):1563-8.
18. Demyttenaere K. Noncompliance with antidepressants: who's to blame? Int Clin Psycopharm. 1998;13(suppl.2):S19-S25.
19. Reid D, Abramson M, Raven J, Walters HE. Management and treatment perceptions among young adults with asthma in Melbourne: the Australian experience from the European Community Respiratory Health Survey. Respirology. 2000;5:281-7.
20. Jacox A, Carr DB, Payne R. New clinical-practice guidelines for the management of pain in patients with cancer. NEJM. 1994;(9):651-5.
21. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther. 2001;23:1296-1310.