Adherence in the treatment of osteoporosis

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Summary
Therapeutic compliance is of great importance if the demonstrable efficacy of drugs is to be reproduced in clinical practice. It has been sufficiently demonstrated that there is a lack of adherence in the pharmacological treatment of osteoporosis. The factors which influence this are highly diverse and complex, with some dependent on the treatment itself, whether in the drug (efficacy, secondary effects) or in its administration regime (frequency, mode of administration). The appearance of every day more efficacious drugs, with more spaced out administration periods and modes of administration which reduce undesirable secondary effects, diminish considerably the rate of abandonment of treatment for osteoporosis. However, these improved drugs should be complemented with an appropriate doctor-patient relationship, aimed at instructing and educating the latter and at maintaining their interest, to achieve a proper adherence to treatment, and thus, the maximum efficacy of the drugs.

Introduction. The size of the problem
The importance of osteoporosis lies in the fact that it predisposes the appearance of fractures, which means that it constitutes a major health problem. The fractures most commonly associated with osteoporosis are vertebral, hip and the distal radius, or Colles, fractures. It has been estimated that the risk of a patient with osteoporosis of suffering any fracture during the rest of their life varies between 40-50% in women and between 13% and 22% in men, and, in the specific case of hip fracture, the risk for a white woman is 17.5%, while for a man it is 6%.

All these fractures have a high level of morbidity and result in a high social-health cost: for example, approximately 25% of vertebral fractures and practically all fractures of the hip require hospitalisation. But, in addition, osteoporotic fractures, especially of the hip, have a considerable mortality. Indeed, studies carried out in this country show that at the end of one year after a hip fracture approximately 30% of patients have died, increasing to 40% when the follow up is extended to two years. Other studies have described a reduction in survival at 5 years of 15% after a hip fracture, observing that the greater part of the deaths occur in the first six months after it.

Osteoporosis is a chronic process, usually asymptomatic, which deteriorates the bone, making it susceptible to fracture. The ultimate objective in the treatment of osteoporosis is to minimise the risk of suffering new fractures. There is no drug which reduces this risk to zero: most of the drugs available nowadays for the treatment of osteoporosis obtain reductions of between 40% and 65%, even when the medication is taken continuously during a period of time which varies between 3 and 5 years. These circumstances (lack of symptoms, necessity for prolonged treatment) means that, as happens with other similar diseases (arterial hypertension, hypercholesterolemia, diabetes mellitus), the abandonment by the patient of their medication is common, and for many diverse reasons. Institutions such as the World Health Organisation and the American Heart Association recognise that one of the main problems in the treatment of chronic diseases in developed countries is non-compliance on the part of patients in the correct taking of their medicines.

With reference specifically to osteoporosis, multiple studies have demonstrated deficiencies in adherence to treatment by patients, and this has
been studied with all drugs used: calcitonin, oestrogen therapy, raloxifene, teriparatide and biphosphonates\textsuperscript{17-22}, and some have even compared the abandonment of osteoporosis treatment depending on which drug is being used. The existing works are highly varied, and often have contradictory results\textsuperscript{23-26}. The disparity in the populations studied and the methodologies applied explain the difficulties in comparing results. However, all these studies agree on the fact that adherence to osteoporosis treatment is, in general, low, and that in the first year the percentage abandonment is found to be between 30% and 50% in most cases.

**The success of treatment for osteoporosis depends on a great extent on adherence**

It is evident that those patients who take their medicine for osteoporosis regularly have better results, both in reference to changes in bone mineral density\textsuperscript{27}, and, more importantly, in the reduction of the rate of fractures and a decrease in mortality\textsuperscript{28,29}. A study carried out by Siris et al. in a broad population of postmenopausal women of over 45 years of age, for whom had been indicated a biphosphonate as a treatment for osteoporosis, showed that, after 2 years of follow up, those women who took the treatment correctly (43%) had a reduction of risk of fracture, both vertebral and non-vertebral, 21% higher than those patients who did not correctly follow the treatment\textsuperscript{30}. Earlier, Caro et al. had obtained similar results, finding a reduction in the appearance of new fractures higher (16%) among those patients who were compliant, as opposed to those who were not. In this study the period of follow up was also 2 years, and the drugs evaluated were calcitonin, hormone replacement therapy and biphosphonates\textsuperscript{31}. The same authors repeated the study, using a broader database, with a cohort of more than 38,000 women affected by osteoporosis, and obtained similar figures: poor adherence to treatment was associated with an increase in the risk of fracture of 17% after a follow up of 1.7 years\textsuperscript{32}. These results are corroborated by those obtained in other studies\textsuperscript{33,34}.

The appropriate adherence to treatment is not only beneficial for the health of the patients, but also results in improved cost-effectiveness for the drug therapy for osteoporosis\textsuperscript{35}.

**The importance of the frequency of administration in the adherence to treatment for osteoporosis**

Poor adherence to treatment for osteoporosis is dependent on many factors\textsuperscript{36,37}. We have already indicated at the start that low or zero symptomology of the disease, and its being chronic, are two of the most important. Other factors which have an influence on adherence are patient-dependent: age, state of health, socio-cultural position. Others are dependent on the medical action taken (motivation, follow up, carrying out of tests which identify the state of the disease). And finally, there are factors dependent on the type of drug used in the treatment: secondary effects, efficacy, mode and frequency of administration. Therefore, adherence is complex and difficult to quantify\textsuperscript{38}. The modification of the factors which negatively influence treatment compliance is one of the objectives all professionals should have when antosteoporotic therapy is prescribed.

Up until now, the main interest in improving adherence has been centred on drug-dependent factors. In general, the drug treatments for osteoporosis have few secondary effects, and only a few infrequent effects could be considered to be serious. On the other hand, over time ever more efficacious and powerful drugs have been developed, varying the modes of administration and lengthening the frequency of dosage, all intended, ultimately, to improve adherence\textsuperscript{39,40}.

**The biphosphonates and adherence in the treatment of osteoporosis**

The biphosphonates constitute the group of drugs most used in the treatment of osteoporosis\textsuperscript{41-43}, and are considered to be the first choice for the treatment of osteoporosis in our ambit\textsuperscript{44}. The gastrointestinal secondary effects of the biphosphonates, the motive for abandonment of treatment in a high percentage of cases\textsuperscript{45}, necessitated the finding of preparations whose administration was more spaced out, and whose mode of administration was different from oral: what were initially daily doses became weekly administration in the case of alendronate\textsuperscript{46} and risedronate\textsuperscript{47}, and monthly oral administration became quarterly intravenous in the case of ibandronate\textsuperscript{48}. The last biphosphonate to be marketed for the treatment of osteoporosis, zoledronate, is for annual, intravenous administration\textsuperscript{49}, which ensures, at least, compliance and therapeutic efficacy over a year, which is very important in view of the high number of abandonments of treatment which happen over this period\textsuperscript{50-52}.

So, all these changes in the administration regimes of the biphosphonates can improve adherence in the long term drug treatment of osteoporotic patients\textsuperscript{53-55}. The beneficial results of this have been demonstrated in different studies. Penning van Best et al. used a database in the Netherlands of the dispensation of drugs over a year, and found that, of 2,124 women who started therapy with biphosphonates, 51.9% of those to whom the drugs were administered weekly continued treatment, but only 42% of those taking a daily dose continued treatment, with different types of biphosphonates used (etidronate, alendronate or risedronate)\textsuperscript{56}. Cramer et al. studied 2,741 women in treatment with biphosphonates and observed that, at the end of a year, persistence was 44.2% in those who had taken the biphosphonates weekly, as against 31.7% among those who took them daily\textsuperscript{57}.

In another study carried out in the United States, Ettinger et al. analysed the sale of prescriptions of alendronate and risedronate in more than 211,000 women. They found that, at the end of a
year, 56.7% of those patients who had taken biphosphonates weekly continued to receive the drug, as against 39% of those who had taken it daily. However, the authors noted that more than 40% of patients did not continue with treatment with weekly biphosphonates, and suggested that formulations which allowed a more spaced out administration could improve therapeutic compliance65. Cramer et al. in a work carried out in a total of 15,640 women in the United Kingdom, France and the United States, found that after a year, the persistence of patients with biphosphonates was higher in those who received the medication weekly, compared to those who received it daily: 44% vs 32% respectively in the United States; 52% vs 40% in the United Kingdom; and 51% vs 44% in France; in all cases the value of p < 0.00166.

In the study known as PERSIST, adherence to treatment at 6 months in a group of women who received ibandronate monthly was compared with another group which took alendronate weekly, and it was found that 56.6% of those who took the monthly treatment continued with treatment as opposed to 38.6% of those who took alendronate weekly66. We have not found a study which compares the adherence to treatment between biphosphonates with an annual dose and those administered more frequently.

On the other hand, there are studies whose objective was to record the preferences of patients with osteoporosis in respect to the pharmacological preparations for their treatment, in which it was observed that, as a general rule, patients prefer a more spaced out administration of treatment65,67. A multicentric, randomised, double blind study carried out by McLung et al. to assess the safety and efficacy of a single intravenous dose of 5 mg of zoledronic acid vs 70 mg of alendronate taken orally, weekly, carried out in 225 women with postmenopausal osteoporosis who had previously received weekly treatment with alendronate, found that 78.7% of patients expressed their preference for an annual intravenous treatment as opposed to a weekly oral treatment65, equal to that stated by the majority of patients participating in a similar study carried out by Saag et al.67.

However, although a higher adherence to treatment is seen with doses at longer intervals, it is notable that almost all the studies also conclude that the percentage of patients receiving the correct medication is sub-optimal, and this is the case whatever the mode of administration. This indicates that, as we have suggested earlier, therapeutic compliance in osteoporosis is complex, and dependent on diverse factors not only related to the drug, but also to the patient and their surroundings, as well as to the medical action taken. A review by Cochrane, Hayes et al.48 indicates that patients take approximately half the medication prescribed. Analysing a series of interventions taken to increase adherence to treatment, they found that those that were sure to be efficacious in the long term were complex to implement. Included amongst these interventions were provision of detailed information, self-monitoring by patients, advice, telephone reminders, family support and psychological treatment. But they concluded that, taken as a whole, the results were rather poor, recommending that new studies dealing with the improvement of adherence to treatment be carried out.

In view of these results, it is evident that the inclusion in the therapeutic arsenal for osteoporosis of more powerful drugs, which can be administered at greater intervals of time and in ways which cause fewer secondary effects, increase considerably adherence to treatment. But we should not forget that in conjunction with these improved drugs we should address other adherence factors related to the patients themselves, as well as proceeding with medical/health interventions which support and promote therapeutic compliance.

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