# Review

# Optimising bisphosphonate treatment outcomes in postmenopausal osteoporosis: review and Italian experience

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**ABSTRACT**

*This review aims to investigate ways to optimise treatment outcomes with bisphosphonate therapy of osteoporosis in general, and in Italian clinical practice specifically.*

*Overall, poor adherence to bisphosphonate therapy is a major limiting factor in the treatment of osteoporosis, and is associated to a large extent with gastrointestinal adverse events. An improved patient-doctor relationship and patient motivation are critical factors to improving adherence. However, other medical interventions also play a significant role. Intermittent dosing regimens decrease gastrointestinal adverse events and improve adherence, and demonstrate at least equivalent efficacy to daily regimens. Intravenous formulations also improve gastrointestinal tolerability, and are recommended in Italy for patients at high risk of this adverse event.*

*Other recommendations in Italy to improve treatment outcomes include a case-finding approach to identify patients most suitable for bisphosphonate therapy, thus reducing the numbers needed to treat to avoid fractures. To facilitate this, a comprehensive assessment is advocated which incorporates bone mineral density, previous fractures, parental history of fractures, corticosteroid use and the presence of other diseases associated with secondary osteoporosis.*

## Introduction

The past three decades have seen an increasing use of bisphosphonates (BPs) for the treatment of osteoporosis (OP) because of their ability to increase bone mineral density (BMD), suppress bone turnover markers (BTM), maintain or improve mechanical bone strength and, ultimately, reduce the number of fragility fractures (1). Given the established efficacy of BPs in OP, attention has turned to other ways to optimise treatment outcomes with these drugs, and the most salient amongst these is the problem of poor adherence to treatment.

OP, which is asymptomatic until a fracture occurs, may be said to present a perfect scenario for poor adherence: it is a long-term disease affecting mainly elderly individuals, and it involves chronic, costly treatments with intensive dosage regimens that may be complicated by adverse effects. The patient perceives no subjective improvement with drug therapy, and the only visible assessments of efficacy are densitometric measurements which require long intervals between revaluations, during which the patient may have already discontinued treatment.

This article reviews the impact of poor adherence to BP therapy on treatment outcomes in OP, and explores the usefulness of extended dosing intervals to improve adherence and thus outcomes, with a focus on the Italian scenario. The different levels of evidence that support such intermittent regimens are examined and compared with that for daily schedules, and safety issues surrounding different BP regimens and formulations are examined. Lastly, other methods that may assist in optimising the therapeutic response in OP are briefly discussed.

A literature search was carried out using the PubMed online scientific citation database of published, peer-reviewed manuscripts. The key words used for the literature search were: bisphosphonate, postmenopausal osteoporosis, adherence and safety. This search was then integrated, per protocol, with Italian data and with the information coming from the summary of product characteristics (SmPC) of the drugs as sold in Italy (usually translated from the European Medicines Agency SmPC).

**Treatment adherence to BPs**

Patient non-adherence to prescribed medication is a phenomenon with significant health and economic consequences. Non-adherence to therapy is estimated to account for between 33% and 69% of all hospitalisations in the United States (2), with consequent expenditure. However, only recently precise definitions for the description of this phenomenon have been established (3), *i.e.* adherence, persistence and compliance, which historically were used interchangeably and inconsistently, thus creating confusion.

Many studies have attempted to identify the factors predicting poor adherence. The main finding is that those predictive factors which can be easily detected such as age, gender, socioeconomic status, cultural level, degree of comorbidity and quantity of drugs taken by the patient show clear differences across various studies (4). The most important factors are the amount of information given to the patient regarding the disease and medication, and above all the personal motivation of the patient (5).

Data show that limited adherence to BPs is often accompanied by an increase in the number of fractures, hospitalisations and related costs (6). However, it must be pointed out that non-adherent patients are likely to be those predisposed to fractures (*e.g.* because of greater comorbidities, multiple therapies and higher pharmaceutical expenditure), and some methodological limitations may be identified, for example the variables which describe adherence are often considered dichotomous but are in fact continuous (7). Large observational studies have demonstrated that less than 6 months of BP therapy does not reduce the probability of incurring a fracture (8). However, over a 24-month period the likelihood of a fracture begins to decrease when a pharmacological coverage of at least 50% is attained, and above this level the risk of fracture decreases exponentially with increased adherence (9).

It has been proven that around 50% of patients abandon their OP treatment during the first year (10). In an attempt to overcome this impediment to effective treatment, more convenient intermittent formulations have been developed, with an improvement in patients' adherence (11). However, currently available BPs differ in physicochemical and biologic characteristics that affect the attainable dose-free interval (12); moreover, fracture reduction by the administration of an intermittent dosing regimen has only recently been shown for some molecules (13, 14). Differences in affinity and osteoclast inhibition affect the ongoing biological action of BPs, which may also be influenced by patient-related variables such as the level of bone turnover and renal function (Fig. 1). The remaining two variables affecting drug availability – dose and dose interval – are inversely related: therefore, an extended dose interval must be compensated by an increased dose to provide a sustained pharmacological effect.

Some reports show that changing from daily to weekly administration of BPs leads to greater persistence with treatment, although adherence remains largely unsatisfactory even with a weekly regimen (15). Observational studies show that a significant percentage of patients abandon BP treatment because of gastrointestinal (GI) adverse effects (16, 17), despite comparable tolerability to placebo was shown in phase III studies. Indeed, therapeutic persistence with BPs after one year seems to be mainly dictated by the occurrence of GI adverse effects and the interval between consecutive administrations (18), which appear to be inversely related. Just as weekly dosing is associated with better tolerance and a greater level of adherence compared to daily administration (15), monthly ibandronate is better tolerated than weekly BP treatment (18, 19). Similarly, in an analysis of around 4000 women, those undergoing monthly ibandronate therapy were 37% less likely to be non-persistent than those receiving weekly BP doses (20).

The analysis of medical claims from an Italian prescription database indicated that, compared to ibandronate group, patients on risedronate and strontium ranelate were at higher risk of treatment discontinuation after the first prescription (21). The analysis was based on an electronic database (LPD-CSD database) of prescriptions given in 2007 and 2008 by a sample of 700 general practitioners (GPs) evenly distributed over the national territory, selected by geographical region, age, gender in order to be representative of all GPs. For each patient, information on the prescription of osteoporosis drugs covered by the Italian Health Care National Service, according with the so called Nota 79 (22). The study included all women who received a first prescription (index prescription) for weekly risedronate, monthly ibandronate or daily strontium ranelate in 2007 or 2008. Persistence and compliance were assessed as follows: non persistent were classified the patients who did not receive other prescriptions after the first index prescription. Among persistent patients, compliant were defined the patients who received a prescription (equal to two monthly packages) for the same drug at least once every 3 months (compliance or medication possession ratio, MPR, >70%), while non compliant were classified the patients with a MPR <70% or switched to one of the other 2 treatments. The results are summarised in Figure 2 reporting the total number of patients participating in the study for each drug and the proportions for no-adherents, compliant and non compliant. Compared to the ibandronate group, patients on risedronate and strontium ranelate were at higher risk of treatment discontinuation after the first prescription. The OR's were 1.43 (CI=1.36–1.49) and 2.18 (CI 2.09-2.28), respectively (Fig. 3). Treatment compliance was also different in the 3 groups, with the best results being seen with ibandronate. The ORs of poor compliance compared to ibandronate were 2.38 (CI 2.2 7–2.49) and 3.69 CI (3.50–3.90) for risedronate and strontium ranelate, respectively (Fig. 3). These findings indicate that monthly ibandronate ensures better treatment persistence and compliance than weekly risedronate and daily strontium ranelate, and are likely to influence the "real-life" use of these treatments with a strong impact in the pharmaco-economic evaluation.

### Safety of different BP formulations and regimens

In RCTs, no differences in GI adverse events between oral BPs and placebo were reported (23). Nevertheless, GI events represent are one of the most common reasons for discontinuation of daily or weekly oral BP treatment in Italy (17) despite labelled dosing instructions (24). This observation may be attributed to several factors including improper drug administration, reporting bias due to warnings of possible GI adverse effects, background incidence of GI disorders, and GI toxicity of the drug itself. In Italian clinical practice, concerns for the onset of GI events have frequently interfered with treatment (17) and patients taking gastroprotectors (common in OP) are at particularly high risk of poor compliance (17).

In pivotal placebo-controlled trials of ibandronate (14, 25), no differences in GI adverse events were observed between groups, even though patients with pre-existing GI disturbances or taking concomitant anti-ulcer drugs or NSAIDs (not infrequent in patients with vertebral fractures) were not excluded. Reducing the frequency of the contact between BPs and the upper GI tract might diminish the risk for and severity of such events (26). Therefore, in extended dosing regimens any potential increase in GI events associated with the higher monthly doses may be counterbalanced by a reduction in the frequency of administration. Indeed, extending the dosing interval with monthly oral ibandronate increased treatment adherence in patients who previously discontinued daily or weekly oral BPs due to GI intolerability (18, 27). Other studies have documented reduced GI events and improved adherence with weekly *vs*. daily (28) and monthly *vs*. weekly BP regimens (19). Thus, monthly BP treatment may be preferred by physicians for patients at high-risk for GI events or those receiving multiple treatments (such as the elderly), in whom good tolerability has also been confirmed (29).

GI toxicity is a local rather than systemic effect, leading in Italy to the recommendation of IV BPs (ibandronate or zoledronate) for postmenopausal

$$\text{Efficacy} = \frac{\text{Dose} \times \text{Biological potency} \times \left(\frac{\text{Turnover} \times \text{Binding affinity}}{\text{Renal function}}\right) \times \frac{\text{Reuptake}}{\text{Desorption}}}{\text{Interval between doses}}$$

**Fig. 1.** Mechanisms of action of bisphosphonates – potential variables influencing efficacy

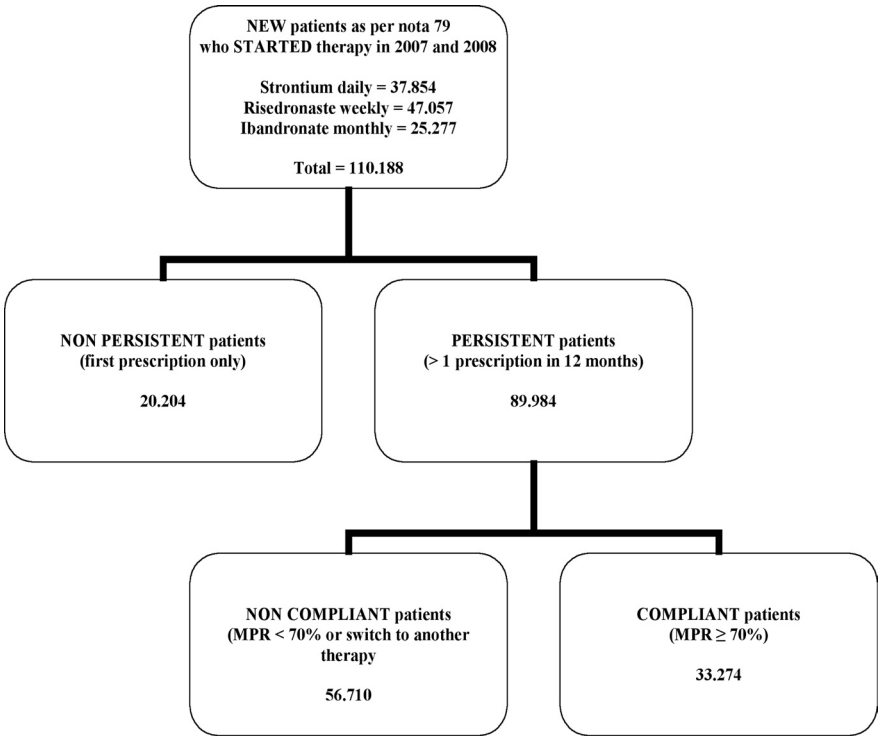


**Fig. 2.** Adherence to oral osteoporosis treatment in the Italian Clinical Practice. Study flow chart with the total number of patients included for each drug, persistent and compliant or not (21).

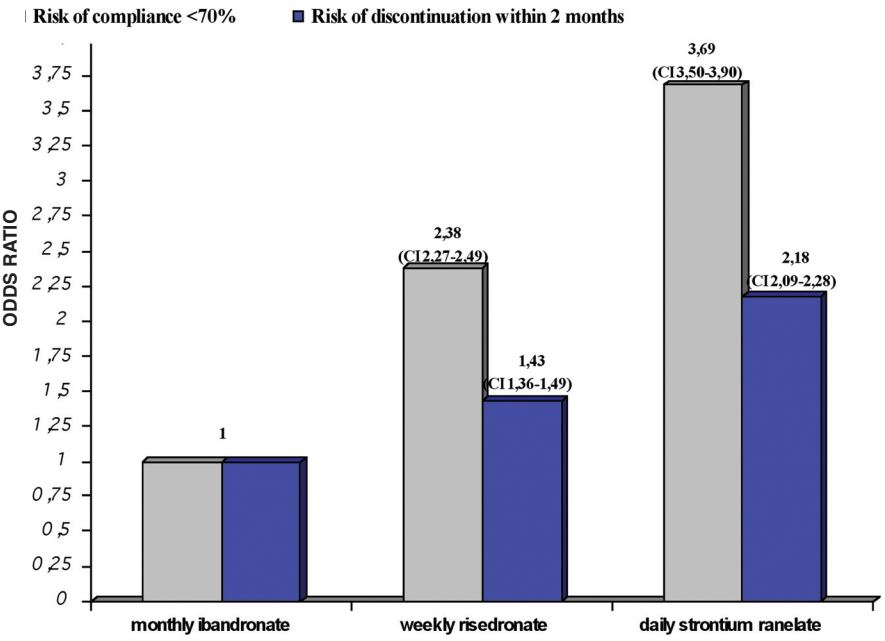


**Fig. 3.** Risk of low compliance or discontinuation in women receiving a first prescription of monthly ibandronate or weekly risedronate or daily strontium ranelate (odds ratio *versus* ibandronate) (21).

OP treatment in patients with GI contraindications or adverse events (30). Moreover, it has been observed that IV ibandronate provides pain relief for patients with corticosteroid-induced osteoporosis or localised transient osteoporosis (31). Similar effects can be found for other BPs in fractured women (32-35). Intramuscular BPs (clodronate or neridronate) are also commonly used in these conditions, although their anti-fracture efficacy needs further investigation. Transient flu-like symptoms (acute-phase reaction or APR) sometimes occur following IV administration of nitrogen-containing BPs (36). APRs generally resolve within 3 days from administration, but may last from 7 to 14 days and require acetaminophen, NSAIDs or corticosteroid treatment. However, no clinical sequelae have been observed in more than 20 years since APR was first reported, therefore the main responsibility may be to provide patients with appropriate information. Italian data (37) suggest that low 25OH-vitaminD serum levels may promote APR symptoms, supporting the practice of giving an oral bolus of 300,000 IU of cholecalciferol two weeks before IV BP treatment.

Prescribed doses of oral BPs have not adversely affected renal function in patients with baseline creatinine clearances ($CL_{CR}$) >30 ml/min. Although the product labelling advises clinicians to avoid BP use in patients with $CL_{CR}$ <30 ml/min, clinical experience in these patients is still scant; in two post-hoc analyses of pivotal risedronate and alendronate registration trials, the use of approved doses for 2 to 3 years did not alter renal function in postmenopausal women with $CL_{CR}$ values as low as 15 mL/min (38, 39). In patients receiving IV BPs the risk of kidney damage is limited and can be further reduced by ensuring adequate hydration and using appropriate infusion times. Both IV ibandronate and zoledronate appear to have a safe renal profile in osteoporotic postmenopausal women with GFR >30 ml/min (40, 41). The lack of head-to-head comparative data between ibandronate and zoledronate in patients with OP precludes knowing if one intravenous bisphosphonate is safer than the other (42). Ibandronate may have a safer renal profile in cancer patients (43). There are evidences that ibandronate, but not zoledronate, is not nephrotoxic in patients with abnormal baseline kidney function (44-48). The better renal safety profile of ibandronate as compared with zoledronate is poorly understood. It might simply be related with the lower bioactive dose given as a single infusion It was also suggested that in the lower nephrotoxic potential of ibandronate may be related to pharmacokinetic differences (49). Compared to pamidronate and zoledronate, ibandronate is more highly protein bound (87% *vs*. 56%), which may limit renal exposure to free drug. In addition, the renal tissue half life of ibandronate is much shorter than zoledronate (24 days *vs*. 150–200 days, respectively). In Italy, a local regulatory commission has indicated that IV ibandronate is preferable to zoledronate for patients with chronic renal insufficiency, or at risk of this condition, as these patients require multiple treatments (50). In patients with severe renal impairment the dose has to be adjusted in order to maintain the same bio-activity (42). Nevertheless, IV ibandronate labelling indicates that an appropriate assessment should be performed in at-risk patients, and that subjects with end-stage renal disease may experience fractures due to osteomalacia or adynamic bone disease, for which BP use is currently contraindicated.

BP therapy for malignant diseases, using dosages dozens of times higher than those for OP, is associated with an increased risk (1–11%) of osteonecrosis of the jaw (ONJ), a syndrome which may be best described as osteomyelitis almost always connected with an actinomycetes infection (51). This adverse effect occurs much more rarely (1/10,000–1/100,000) in patients undergoing BP treatment for OP (52), and therefore a causal relationship is more difficult to establish. Taking into consideration the limitations of spontaneous reporting of adverse effects, between 2001 and 2007 only 18 cases of ONJ (15 with alendronate and 3 with risedronate) were communicated to the Agenzia Italiana del Farmaco (Italian Drug Administration, AIFA), with an estimated frequency <1/100,000 exposed individuals per year. A recent publication about the risk of ONJ, jointly written by the Italian Society for Osteoporosis, Mineral Metabolism and Skeleton Diseases and the National Association of Italian Dentists, officially endorsed by the Italian Minister of Health, is trying to standardise practices in Italy (53). In brief, it is recommended that patients with OP are informed about the benefits and risks of BP therapy, including ONJ, and that they should pay special attention to their oral state and hygiene. They should inform their dentist prior to starting BP therapy, keep their doctor informed of any changes in dental condition, and some special precautions may be warranted for invasive dental procedures.

Recently a warning has been raised about atypical fractures during long-term BPs therapy. Atypical femoral fractures are most commonly observed in the proximal one-third of the femoral shaft, but may occur anywhere along the femoral diaphysis from just distal to the lesser trochanter to proximal to the supracondylar flare of the distal femoral metaphysis. However, based on published and unpublished data and the widespread use of BPs, the incidence of atypical femoral fractures associated with BP therapy for osteoporosis appears to be very low, particularly compared to the number of vertebral, hip and other fractures that are prevented by BPs. Moreover, a causal association between BPs and atypical fractures has not been yet fully established (54).

## How targeting patients most suitable for BPs treatment?

In 2002, more than 86,000 femoral fractures were registered in Italy in patients aged >45 years (a 9% increase compared with 1999); 77% were female and 80% were >75 years of age (55). The direct costs of hospitalisation in those aged >65 years alone (n=80804) were almost 400 million Euros (an increase of 15% compared with 1999); when rehabilitation, social aid and other indirect costs are considered, the cost estimation for hip fractures due to age-related OP was over a billion Euros

in 2002 (55), comparable to costs for acute myocardial infarction (56). Since 2002, further increases in the number of femoral fractures in subjects over 65 years were observed in each year until 2005 (n=94,471), when a reduction or at least a stabilisation in the incidence of this event was observed for the first time, in particular in women between 65 and 74 years of age (30.4/10,000 cases in 2002, 33.5 in 2003, 35.2 in 2004 and 34.8 in 2005) (57). This finding may suggest the initial effects of more extensive preventive measures including the use of BPs.

Of note, fractures of the femur, like most non-vertebral fractures and clinical fractures, may occur in osteopenic subjects, while osteoporotic patients may not experience any fracture, due to the stochastic nature of fracture and to other risk factors unrelated to BMD such as previous fracture, smoking, high bone turnover or rheumatoid arthritis. Three fundamental conclusions originate from this assumption.

First, in order to substantially reduce the incidence of fractures in the general population and/or in specific age groups, community prevention interventions should be recommended, including reduction of identifiable risk factors such as anti-smoking campaigns, reduction of falls, promotion of physical activity, nutritional education, and vitamin D supplementation (58), as vitamin D deficiency represents a widespread and serious issue in Italy, particularly in the elderly (59).

Second, a case-finding approach should be used to identify patients eligible to pharmacological treatment on the basis of prevalent fragility fractures or very low BMD; this approach would result in a low number needed to treat (NNT) in order to prevent a fracture and avoid unnecessary adverse events. The AIFA endorses this approach (22), guaranteeing reimbursement for patients with previous vertebral or femoral OP fractures or those with severely reduced BMD (T score < -4 or < -3 if associated with other risk factors) (Fig. 3), *i.e.* when the risk of relapse within a decade is >10% and the NNT to prevent a vertebral fracture (between 10 and 20) is considered acceptable.

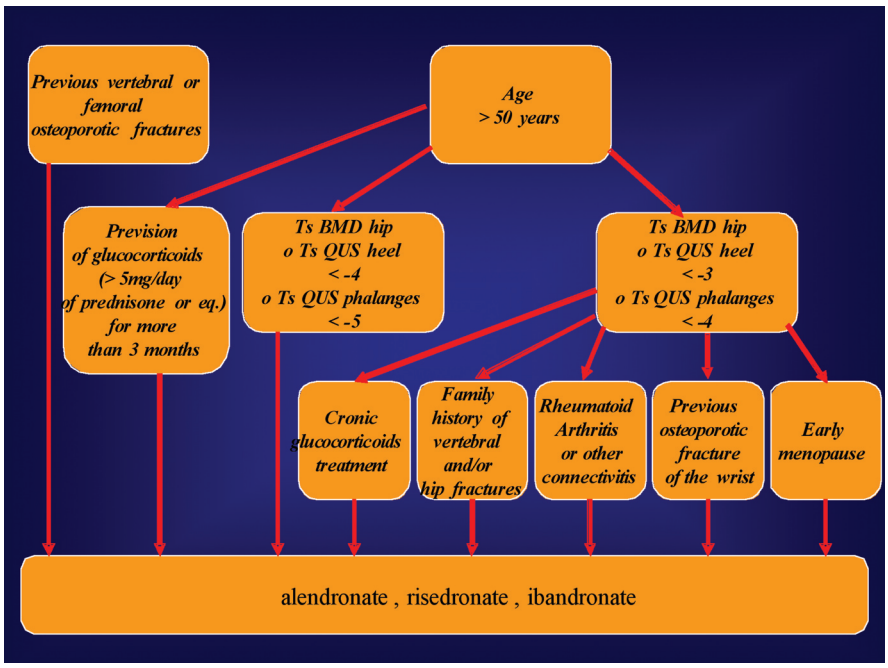


**Fig. 4.** Indications believed to be appropriate for treatment with oral BPs, which are reimbursable by the Italian National Health Service (47).

Third, the possibility to predict fractures on the only basis of BMD is limited; this information must be integrated with the history of the patient and other clinical details. An initial international attempt to address this need is represented by the Fracture Risk Assessment Tool (FRAX) (60), which quantifies the risk of principal fractures over a 10-year period using the BMD, age, body mass index and another seven dichotomous variables (*i.e.* previous fragility fractures, familiarity with environment for hip fractures, ongoing corticosteroid treatment, rheumatoid arthritis, smoking, alcohol abuse, and some concomitant diseases associated with OP). Although the FRAX tool represents a major step forward in the management of OP, it does have some significant limitations, and its lack of flexibility may limit its use in some countries, like Italy, as recently suggested (61).

The risk of fracture may be estimated by FRAX without including BMD, and this may be considered unacceptable in countries such as Italy where bone mass assessment devices are readily available. In fact, the specificity of other risk factors for OP is not high and there are no data demonstrating a reduction of risk of fractures of any pharmacological treatment in patients without significantly low BMD or prevalent vertebral fractures. FRAX without BMD might be used to select patients in whom densitometry is warranted, but in Italy an alternative and more detailed tool is already available and being used (Livelli Essenziali di Assistenza, LEA, Essential Assistance Level for densitometry) (62). Another limitation of the FRAX is the lack of definition of type, severity and number of previous fractures. In Italy, since 1998, a prevalent vertebral or femoral fragility fracture has been considered a strong indication for treatment, independent of BMD, and more recently the number and grade of vertebral fractures have also been considered (22). Moreover, with FRAX the risk associated with previous corticosteroid therapy is not adjusted according to dose, and the parental history of vertebral fracture is not included as a risk factor. These limitations are relevant in Italy for the application of the "Nota 79" issued by the AIFA, which outlines the conditions for the full reimbursement of drugs for the treatment of osteoporosis (22) (Fig. 4). Further, FRAX includes only rheumatoid arthritis and not other diseases leading to secondary osteoporosis, which may represent important risk factors. Last,

quantitative ultrasound (QUS) assessments are not included in the FRAX; however for some patients only QUS devices are available, and in Italy both QUS and dual x-ray absorptiometry are widely used and their result is considered in the current reimbursement policy of the Italian Health Care National Service (Fig. 4).

With regards to medication, as shown in Figure 4, AIFA recognises anti-resorptive drugs as first-line therapies, and includes amongst these three BPs with recognised effectiveness (alendronate, risedronate and ibandronate). In Italy, the use of IV zoledronate and ibandronate is limited to the hospital environment; in some regions, these treatments can be prescribed only to patients intolerant or with other contraindications to oral BPs. The difference in the monthly cost of BP therapy for alendronate, risedronate and ibandronate, should be assessed in view of the demonstrated improvements in compliance, and therefore possibly in effectiveness, of monthly ibandronate treatment (21, 63). The AIFA recommends that the prescription of anabolic treatment (teriparatide or parathormone), associated with high costs and uncertain safety profiles, must be limited in terms of duration (18 months). Moreover, this treatment should be administered only in specifically-qualified Centers to patients with severe OP who carry an extremely high risk of new fractures (22).

## Which approaches to optimising treatment response?

Few studies have investigated the optimisation of therapeutic response to BP therapy, including the use of supplements. However, a study performed in Italy demonstrated that the risk of an inadequate clinical response increased is almost doubled in patients who were not taking calcium and vitamin D supplements correctly, compared to those with a compliance greater than 50% ($p<0.001$) (64). A similar effect of supplementation on optimising increases in BMD was observed in other studies (65-67).

In daily clinical practice, inadequate BMD or bone turnover markers responses to therapy may be affected by a number of factors including adherence to therapy, adequate supplementation of calcium and vitamin D, adequate physical activity, and the exclusion of other co-morbidities or concurrent treatments which could affect skeletal health. In the case of intestinal absorption problems, for example, the therapeutic efficacy may be maintained using IV preparations of BPs (68, 69). It must also be pointed out that some studies have shown a reduction in new fractures even when there is a tendency toward reduction of BMD, probably related to favorable modifications of skeletal turnover (70), and that the occurrence of a new fracture may not necessarily be interpreted as a therapeutic failure; had the patient not taken the drug, the severity or quantity of fracture could have, in fact, been greater.

There are limited long-term data on the antifracture effectiveness of BPs. There appears to be no loss of efficacy during 10 years' alendronate (71) or 7 years' risedronate treatment (72), while the FLEX (Fracture Intervention Trial Long-term Extension) study demonstrated that patients who discontinued alendronate after 5 years had an increased risk of clinical vertebral fractures, compared with those who continued treatment for 10 years (73). A post-hoc analysis of this study suggests that continuous treatment for ten years reduces risk of non vertebral fractures in patients without vertebral fractures who continue to have osteoporotic t-scores of the femoral neck after five years of therapy (74). The uncertainty over optimal duration of treatment stems, in part, from doubts concerning the real value of reduction in skeletal turnover after the long term administration of BPs and the rising risk of adverse events (such as ONJ) with continuous long-term therapies. The decision whether or not to continue BP therapy after 5–7 years must be taken on a case by case basis after new assessments of fracture risk including clinical, densitometric and skeletal turnover evaluation (75). If the risk of fracture has substantially improved and no new fractures have occurred, a treatment vacation lasting 12 months should be considered after each 5-7 years of continuous therapy.

## Conclusions

There has been notable progress in the pharmacological treatment of OP over the last two decades, such that patients with skeletal fragility now have a variety of effective therapeutic choices that may be tailored to individual preferences. Therefore, other factors such as therapeutic adherence, adverse effects and costs now play a larger role in the choice of medication.

Non-adherence has been demonstrated to play a major role in poor treatment response to BPs, leading to more fractures. Of paramount importance in improving patient adherence is doctor-patient communication and patient motivation. However, GI adverse events are also a major contributor, and intermittent regimens have been shown to reduce these events and thus improve adherence. Extended-dose regimens have demonstrated at least equivalent efficacy to daily regimens with improved GI tolerability, and may be preferred for patients at high risk of this adverse event. IV formulations also avoid GI toxicity and may be useful for patients with GI contraindications. Of note, further efforts are still required to identify patients at particularly high risk of fracture, in order to reduce the NNT to an acceptable level and further optimise the cost/effectiveness of BPs treatment.

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