Safety profile of drugs used in the treatment of osteoporosis: a systematical review of the literature*

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SUMMARY

The range of osteoporosis treatments is increasingly large and, like any disease, the pharmacological management of patients should involve a risk/benefit evaluation to attain the greatest reduction in risk of fracture with the lowest incidence of adverse events. The aim of this review is to critically appraise the literature about the safety issues of the main pharmacological treatments of osteoporosis. This document is the result of a consensus of experts based on a systematic review of regulatory documents, randomized controlled trials, meta-analyses, pharmacovigilance surveys and case series related to possible adverse drug reactions to osteoporosis treatment with calcium and vitamin D supplements, bisphosphonates, strontium ranelate, selective estrogen receptor modulators, denosumab, and teriparatide. As expected, randomized controlled trials showed only the most common adverse events due to the samples size and the short observation time. Case series and observational studies are able to provide data about uncommon side effects, but in some cases a sure cause-effect relationship needs still to be confirmed. Consistently with methodological limitations, the newer drugs have a tolerance profile that has not been fully explored yet. Osteoporosis treatments showed an overall good tolerance profile with rare serious adverse events that, however, must be well known by the clinician who prescribes these drugs. The concern about possible adverse events should be weighed against the reduction of morbidity and mortality associated with a significant fracture risk reduction.

Key words: *Osteoporosis, Treatment, Pharmacology, Side effects.*

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INTRODUCTION

Until a few years ago physician's decisions in drug prescription were only based on personal knowledge and experience, but nowadays a therapeutic prescription should be supported by clinical evidences from the scientific literature. This approach is even more strictly required when the therapeutic goal is the prevention of a clinical event related to a chronic disease. In this situation the therapeutic strategy could be extremely extended in time and a single physician's experience could not obtain a good overlap of the prescribed therapy to the already obtained or possibly achievable results.

In this area, therapeutic decisions on osteoporosis (OP) treatment can be even more difficult: even if a number of drugs with different mechanisms of action has been made available in the last years, data about direct comparisons of efficacy between various therapeutic options are still lacking. Moreover, although a complete evaluation of the safety profile of drugs prescribed in elderly is required due to frequent comorbidities and concurrent treatments, regis-

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tration trials have limited durations up to 3 years, while therapeutic strategies targeted to fracture prevention should be extremely longer.

In the absence of evidences on long-term safety from clinical trials, data from medical literature on this issue are derived from observational post-marketing studies. However it could be extremely difficult to extrapolate the safety profile of the *best therapeutic choice* from these studies because of their low reliability related to the study design. Moreover, the lack or underutilization of national and international registries where drug-related adverse events are collected, does not allow a correct knowledge of the real incidence of these events. A further source of confusion about long-term safety of drugs can be provided by some *marketing strategies* of pharmaceutical industries, which tend to highlight side effects of drugs aiming to influence drug prescription to their advantage.

With the aim of clarifying these issues, a group of experts has been requested by the Italian Society of Osteoporosis, Mineral Metabolism, and Skeletal Diseases (SIOMMMS) to review all the recent literature on this topic, in order to release a document which could provide the physician with the most objective evaluation of the safety profile of available drugs for the prevention of fragility fractures.

CALCIUM

An insufficient calcium intake with a resulting negative calcium balance can lead to a secondary hyperparathyroidism, which can stimulate bone turnover and induce an increased bone loss. In subjects with a reduced calcium intake, calcium supplementation (with or without associated vitamin D) showed an anti-fracture efficacy especially in the elderly and in patients on chronic treatment with corticosteroids. A supplementation with calcium has been systematically prescribed to patients enrolled in studies investigating the anti-fracture efficacy of other drugs.

Calcium supplements and cardiovascular risk

The association between calcium supplementation and the risk of cardiovascular events has been investigated in a number of observational studies and randomized controlled trials (RCT), with conflicting results. In most studies, including a large RCT on 36,000 women with a 7-year follow-up, no significant interactions were found (1-7). Conversely, in 3 studies a higher relative risk (RR) of cardiovascular events related to calcium supplementation was observed in women (8), men and women (9), or men but not women (10), while a single observational study showed a reduced risk (11) even after a 20-year follow-up (12). A recent study showed an increased overall and cardiovascular mortality related to calcium supplementation only in women with a high intake of calcium from diet (>1400 mg/day), which could slightly increase the risk of death by itself (13). Systematic reviews and meta-analyses yielded conflicting results: a non significant modification of cardiovascular risk was found (14-17) as well as a 30% increase of myocardial infarction risk, without consistent variations of the risk of other events such as stroke, sudden death, or a combination of stroke, myocardial infarction and sudden death (18). A supplementation with calcium combined with vitamin D, which is usually recommended (19-21) and prescribed in clinical practice (22), was shown to reduce the mortality from all causes (23), while in other studies was associated with an increased risk of cardio-vascular events (24). Not even the pathophysiological approach contributed to dispel the doubts: calcium supplements were related to a risk factors improvement (16, 25) as well as to potential adverse effects, like an increase in vascular calcifications (26) which however was not confirmed in other studies (27). In conclusion, available data do not provide clear evidences (28). This uncertainty is also related to methodological limitations of the available studies (29), such as those concerning data collection (often self-reported and not confirmed by blinded observers) from trials designed with different

aims (7), results derived from sub-groups analyses (24), interferences with a concurrent assumption of calcium from diet or from other self-prescribed supplements (13), the reduced adherence to the therapy (30), the concomitant assumption of different dosages of vitamin D (30), the assumption of calcium supplements near the meals or in different moments of the day with possible variations in serum calcium levels (13), and the incomplete assessment of concomitant cardiovascular risk factors.

Calcium supplements and nephrolithiasis risk

Beside a certain protective effect of calcium from diet, calcium supplements show equivocal effects on nephrolithiasis risk. An increased risk of nephrolithiasis is mainly supported by a large observational study on more than 91,000 women with a 12-year follow-up (31) and by the *Women's Health Initiative*, a RCT on more than 36,000 women with a follow-up of 7 years (32). In the first study the RR of nephrolithiasis was 1.20 (CI 95% 1.01-1.41), in the second one 1.17 (CI 95% 1.02-1.34) with a moderate increase of absolute risk (2 cases per 10.000 person-years). On the contrary, 2 RCTs did not show an increased risk of nephrolithiasis (5,33), as well as a number of observational studies on about 45,000 men (34,35), 96,000 young women (36) and 78,000 women after menopause (37). A recent systematic review did not show an increased risk of nephrolithiasis in subjects with OP treated with calcium supplements (38).

Also on these issues the literature shows important limitations, largely similar to those described for cardiovascular risk. As the protective effect of calcium from diet is ascribed to a reduced absorption of oxalate in the digestive tract, it could be convenient to take calcium supplements with meals, especially if oxalate-rich (31,37).

Summary of evidences

Data about the association between calcium supplementation and cardiovascular or nephrolithiasis risk are not conclusive.

For prudential reasons, to achieve the calcium intake required for osteoporosis prevention and treatment, it should be recommended to:

- always estimate the calcium needed by every single patient before any prescription;
- try to achieve the adequate calcium intake from diet only;
- prescribe calcium supplements only when a diet modification is not sufficient, advising the patient to take them during meals, and at the minimal dose required to meet patient's requirement.

VITAMIN D

Deficits of vitamin D with a lower extent than those causing rickets and osteomalacia are still responsible for a reduced absorption of calcium in the intestinal tract and may represent a pathogenic way of OP, primarily in the elderly. In the last years a number of studies suggested a possible protective role of vitamin D and its metabolites in the pathogenesis of many extra-skeletal diseases, such as muscle, cardiovascular, autoimmune and neoplastic diseases.

High doses of vitamin D

The administration of vitamin D at high doses once a year in subjects not deficient was associated with an increased risk of falls and fractures. In a RCT on 2256 women treated with colecalciferol 500,000 IU per os for 3-5 years, the risk of falls (RR 1.15; 95% CI 1.02-1.30, P=0.03) and fractures (RR 1.26; 95% CI 1-1.59, P=0.047) was higher in the treatment group than in the placebo group (39). A previous RCT on 9,440 subjects treated for 3 years with 300,000 IU of intramuscular vitamin D2 had shown a significant increase of risk only for specific types of fractures or in subgroups, without a significantly increased risk of falls (40). Both these studies have relevant methodological limitations among whom the main is, according to the authors (41), the inclusion of subjects with basal 25OH-vitamin D levels in the physiological range. A recent RCT investigating the effects of a supplementation with

colecalciferol 150,000 IU every 3 months in subjects not deficient did not show any negative effect on the risk of falls and/or fractures (42). Vice versa, a previous RCT demonstrated favorable effects on falls and fractures of the administration of 100,000 IU of colecalciferol every 4 months for 5 years in 2686 subjects with unknown basal 25OH-vitamin D levels (43). Doses of colecalciferol higher than 600,00 IU were associated with increased levels of markers of bone resorption (44), while this association was not significant from a clinical point of view for boluses of 300,000 IU and absent for doses of 100,000 IU (45). Monitoring serum 25OH-vitamin D levels during supplementation is suggested only for high doses (>1000 IU/day) or when concomitant diseases can induce extremely elevated serum levels of vitamin D (granulomatosis) or enhance the consequences (primary hyperparathyroidism) (46).

Vitamin D metabolites

The use of vitamin D metabolites hydroxylated in position 1 (calcitriol and alfacalcidol) is associated with a significantly increased risk of hypercalcemia and hypercalciuria. This effect is well known and documented and it can be easily explained by an overcoming of the metabolic step that is an endogenous regulator of calcitriol synthesis (47,48). However, serious consequences of hypercalcemia are infrequent (49). If the vitamin D metabolite hydroxylated in position 25 (calcifediol) is prescribed, it should be taken into account that doses in micrograms (μg) or in IU did not match with those of colecalciferol. It has been recently suggested that 1 μg (40 IU) of calcifediol equals 4-5 μg of colecalciferol (50), but more data are requested in different populations of patients with a long follow-up to exactly define the conversion factor between the two molecules.

Summary of evidences

Possible adverse effects related to doses of vitamin D higher than or equal to 300,000 IU, administrated once a year in subjects not deficient, have been reported.

To maintain an adequate vitamin D status, the use of fractionated doses such as daily, weekly or monthly doses is to be preferred. High doses of vitamin D to be taken in a few weeks are currently recommended in deficient subjects to correct the deficit.

A periodic check of serum 25OH-vitamin D levels (*e.g.* every 2 years) should be performed in subjects supplemented with more than 1000 IU/day. Checks should be more frequent in subjects with granulomatosis or primary hyperparathyroidism.

The highest safe dose in long-term treatments is 4000 IU/day.

During pregnancy, when supplementation is indicated, boluses (single doses higher than 25,000 IU) have to be avoided.

Vitamin D metabolites hydroxylated in position 1 (calcitriol and alfacalcidol) can cause hypercalcemia and hypercalciuria and their administration is not recommended in osteoporosis treatment.

■ BISPHOSPHONATES

Pharmacokinetics of bisphosphonates (BP), which are characterized by a high affinity for bone, can explain their overall good tolerability. The low intestinal absorption (less than 1%) even under the best conditions, such as fasting and in association with a large amount of water, causes the achievement of low plasma levels after oral administration. Even if serum peaks can be higher with parenteral administration, they are however transient and short-term. Serum levels of BP quickly decrease due to fast adhesion to bone surface (about 50%); the remaining amount is excreted by the kidney, through glomerular filtration and proximal tubular excretion (51). Skeletal retention of BP is instead extremely prolonged, although it varies depending on bone affinity of the different types of BP. Therefore biologic half-life of BP is long, despite their short serum half-life. A part of the amount released from skeleton can adhere to bone again, while the remainder is excreted by the kidney. Small amounts of BP have been documented in body fluids up to 8 years after the treatment was stopped (52, 53). This finding can justify

caution in BP use in fertile women, even if an association with fetal malformations has not yet been demonstrated in humans (54), but possible interferences on fetal development were observed in animal models.

Acute phase response

Acute phase response (APR) is a transient flu-like syndrome, usually lasting 2-3 days, characterized by fever, myalgias and/or arthralgias, and malaise and which develops in approximately 30% of patients after the first i.v. administration of amino-BP (nBP) (*i.e.* pamidronate, zoledronate, neridronate and ibandronate) (55). Sometimes gastrointestinal manifestations (abdominal pain, nausea, vomiting) or ocular inflammations can occur (56). Despite being rare, APR has been reported also after high doses of oral nBP (ibandronate) (57). It is associated with a rapid reduction of circulating lymphocytes and with an increase of serum levels of C reactive protein (55) and pro-inflammatory cytokines, such as tumor necrosis factors, IL-6 and Interferon-γ (58-60), which is the reason why it is called APR. The rapid overproduction of cytokines is related to γδ T lymphocytes activation by metabolites of the mevalonate pathway, which accumulate after pharnesil-pyrophosphate-synthase inhibition by BP phagocytosed by monocytes (61-63). Serum levels of circulating γδ T lymphocytes are predictive of APR (64) and this observation can explain why this adverse effect is more frequent in young patients, who have a higher number of circulating γδ T lymphocytes. APR does not develop or it is strongly attenuated after further infusions of nBF (51). This is probably related to a reduction in circulating γδ T lymphocytes over time, which has been observed after the first administration of i.v. nBP, especially when associated with an APR (65). It is unknown whether γδ T lymphocytes reduction can be associated with clinically significant immunological effects, either negative or positive, even because it is not clear whether it represents a reduced availability or chronic tissue activation. APR after zoledronate infusion seems to be also associated with a long-term reduction of circulating levels of other lymphocytes subpopulations and eosinophils (66).

APR can be prevented or managed with paracetamol or NSAIDs (67), but not with statins (68, 69) despite their use could be hypothesized with the aim to upstream inhibit mevalonate pathway and consequently reduce metabolites which accumulate after nBP administration (70). Vitamin D deficiency should be also prevented before nBP administration, since it is reported to enhance the risk of APR occurrence (71).

Gastrointestinal side effects

Gastrointestinal side effects, mostly of the upper tract, or even only concern of them, are the most frequent cause of reduced compliance or interruption of treatment with oral nBP, also considering age and comorbidities of treated patients who are possibly affected by gastrointestinal diseases (72). These side effects can be partially prevented by instructing patient to take the medication with a large amount of water and without lying down for at least 30 minutes after taking the drug (73). Moreover the availability of weekly or monthly formulations strongly reduced the frequency of gastrointestinal adverse events by decreasing the probability of repeated stresses to gastro-esophageal mucosa (74-79). These side effects have never been reported after parenteral administration of BP.

A study based on a large English database of clinical prescriptions reported a doubled incidence of esophageal cancer related to oral nBP use for at least 5 years (80), but this finding was not confirmed by a further analysis performed on the same database (81). Even in patients with Barrett's esophagus treated with oral nBP an increased risk of esophageal adenocarcinoma was not observed (82). In 2012 the US Food and Drug Administration declared that, based on current knowledge, no definitive conclusions can be drawn about the relationship between oral BF and esophageal cancer. A recent meta-analysis of observational studies did not find any evidence about the association between oral BP and esophageal adenocarcinoma (83).

Even if the tolerability profile and the gastrointestinal risk are overall acceptable, further investigations are required when dysphagia and retrosternal or epigastric pain are observed in conjunction with oral BP administration.

Hypocalcemia

A transient hypocalcemia with consequent hypocalciuria and secondary hyperparathyroidism is expected because BP are strong inhibitors of osteoclastic resorption, which contributes to physiological release of calcium from bone to bloodstream. However hypocalcemia is usually asymptomatic in the absence of other predisposing conditions, such as a reduced calcium intake and/or low vitamin D levels, hypoparathyroidism or renal failure.

Renal failure

Based on their pharmacokinetics, BP are known to be excreted by the kidney, therefore prescription of these drugs is not recommended when creatinine clearance is lower than 30 mL/min (84). Renal failure was an exclusion criterion in pivotal trials on BP. However, a number of patients with mild renal failure and without alterations of phosphocalcic metabolism were included in trials, so allowing verifying the good tolerability of BP also in these conditions (84-86).

Therefore, even if specific studies on patients with chronic renal diseases are lacking, BP use is allowed also in these conditions but a low dose and/or a reduced frequency of administration are needed (86). In patients with a renal transplantation, even in the absence of evidences of anti-fracture efficacy, BP are usually recommended to prevent bone loss (87-89). It is however noteworthy that in chronic renal failure metabolic bone diseases other than OP can be observed and intravenous BP use can induce an extreme suppression of bone turnover (adynamic bone) (88).

It is also well known that a quick infusion of high doses of BP can induce acute renal failure (90). In a small subgroup of patients with postmenopausal OP, a transient increase of creatinine levels was observed 10 days after an infusion of zoledronate lasting more than 15 minutes (91). It is therefore recommended that patients treated with intravenous BP are properly hydrated and do not take other treatments potentially nephrotoxic.

Because direct comparisons between different intravenous BP do not exist, it is not known whether ibandronate has a safety renal profile different from zoledronate (91).

Oral BP use at registered doses for the treatment of postmenopausal OP does not pose risks in terms of renal function.

Musculoskeletal pain

Even if the association with BP use is still discussed, the onset or a worsening of musculoskeletal pain following alendronate, risedronate or zoledronate administration have been reported, but are usually reversible after treatment interruption (92-94). No convincing physiological explanation has been conceived yet.

Ocular inflammation

Cases of iritis, episcleritis and conjunctivitis have been reported after BP use, especially for intravenous administration and with an incidence up to 1% (95-97). This side effect does not seem to be exclusive of the most recent BP, having been reported also with first generation BP (98). These adverse events can be managed with local corticosteroids. In the most severe cases BP treatment should be interrupted and patients should be discouraged from reintroducing these drugs (99).

Cutaneous manifestations

Rash, itching and urticaria have been reported with BP use, but rarely (100). They do not seem to be a class effect, because these cutaneous reactions can disappear changing BP.

Mucositis and oral mucosa lesions

Rarely, mucositis and oral mucosa lesions have been described but they do not seem to correlate with osteonecrosis of the jaw (ONJ) risk (101).

Usually they were related to an incorrect

modality of drug intake and recovered after treatment interruption or simply complying with drug instructions.

Hepatitis

A few cases of transient hepatitis, documented by liver biopsy, have been reported after alendronate (102) or risedronate (103) treatment for months or years. They recovered after treatment interruption.

Cardiovascular risk

Patients treated with BP usually have an increased cardiovascular risk related to age, comorbidities and OP itself (104,105). In a pivotal study on zoledronic acid a higher incidence of atrial fibrillation was observed as severe adverse event in the treatment group than in the placebo group (1.3% *vs* 0.5%, respectively) (106). This finding was not confirmed in a further trial (1.1% incidence in the treatment group *vs* 1.3% in the placebo group) (107). Post-hoc analyses from the main trials on alendronate, risedronate and ibandronate, which involved about 30,000 patients, did not confirm the association between BP use and risk of atrial fibrillation (108-110). In 2011 the Food and Drug Administration concluded that there were not enough reasons to suspect that OP treatment with BP could induce atrial fibrillation.

On the contrary, a part of mortality reduction which was observed after zoledronate treatment in patients with femoral fractures was ascribed to a reduced incidence of arrhythmias (111). Moreover, a reduced risk of myocardial infarction was recently observed during BP treatment in patients affected by Rheumatoid Arthritis (112).

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) associated to nBP treatment is defined for diagnostic purposes as *the presence of an area of exposed bone in the oral cavity that does not heal within 8 weeks of appropriate treatment, in a patient who currently receives or has been exposed to a BP and has not had radiation therapy to the craniofacial region*. This definition proposed by the American Society for Bone and Mineral Research (ASBMR) Task Force (113) has been implemented in 2009 by the Italian Ministry of Health. Other clinical signs or symptoms can arouse suspicion of an ONJ but do not permit a definite diagnosis (113). Four clinical stages have been defined, with a stage 0.

This staging has been recently modified (114) and it is currently undergoing a further revaluation (115). From a pathological point of view it is a chronic osteomyelitis usually caused by germs of the oral flora, in particular Actinomices. Its pathogenesis has not yet been defined and a number of molecular and genetic factors have been postulated.

Certainly bone turnover suppression and bacterial contamination play a key role (116). In patients with OP the main risk factors for ONJ are a prolonged treatment with oral BP (>3 years for alendronate), uncontrolled diabetes, a treatment with corticosteroids or immunosuppressive agents, and an excessive consumption of alcohol or smoking.

Among local risk factors, tooth extraction, dental and periodontal disease, and incongruous dental prostheses are the main predisposing factors, while implant-prosthetic procedures and dental-alveolar elective surgery are surely less relevant risk factors (117, 118). Because the frequency of ONJ in patients with OP is extremely low, these risk factors are borrowed from a number of case studies on ONJ in patients with cancer. Therefore the level of evidence and prediction of these factors is relatively low (119). ONJ in patients with OP is a rare adverse event. No reliable epidemiological data about ONJ are available in this clinical setting and prospective data are lacking.

The uncertainty is even higher because cases of ONJ have been described also in a population of subjects who have never been treated with BP (120). The first evaluations of incidence made an estimate of 1 case for 10,000-100,000 person/years (113). An Australian survey assessed an incidence between 0.01% and 0.04%, which increased to 0.09-0.34% in patients who underwent tooth extraction (121). These data have been recently confirmed by some

cohort studies (0.02%) (122). The estimated prevalence of ONJ in OP varies from 0.02% to 1% (123).
The most reliable epidemiological data are related to the use of alendronate due to its widespread use (120), while the real incidence and prevalence of ONJ in patients treated with i.v. zoledronate 5 mg/year or ibandronate 4 mg every 3 months can hardly be assessed epidemiologically.
In Italy it is extremely high the concern of dentists, who are often unwilling to perform invasive procedures, above all extractions and dental implants, in patients who have been treated even for a short time with BP for OP or, alternatively, they suggest prolonged drug interruptions before dental works. In 2009 the SIOMMMS in collaboration with the National Association of Italian Dentists (ANDI) produced a *consensus* document on the prevention of ONJ in patients with OP (www.SIOMMMS.it) which was endorsed by the main Italian scientific societies involved in OP management (SIR, SIOT, FADOI, SIRM, SIMFER e CROI). Based on more recent data about ONJ, an update of these recommendations may be useful.
It is interesting to point out that many recommendations based on international literature and reported in guidelines (such as national guidelines by SIOMMMS) are supported by a low level of evidence but by a high strength of recommendation based on experts opinion.
The Ministry of Health produced some recommendations for ONJ prevention in patients with cancer. Recently a document on ONJ related to BP use in patients with cancer and in patients with OP was released by the Italian Society of Maxillo-Facial Surgery (SICMF) and the Italian Society of Oral Pathology and Medicine (SIPMO) (124).

Atypical femoral subtrochanteric/diaphyseal fractures

Atypical femoral subtrochanteric/diaphyseal (ST/DF) fractures are an uncommon adverse event that at the beginning was described in patients subjected to long-term therapy with BP (125,126). These fractures were defined as *atypical* because of their clinical and radiological features, which are different from those of classical or *typical* ST/DF fractures in elderly with OP (125,126). Atypical femoral ST/DF fractures develop spontaneously or after a minimal trauma anywhere in the femur from just below the lesser trochanter to above the supracondylar line.
They can be complete fractures from lateral to medial cortical or incomplete fractures that involve only the lateral cortex (stress fractures). Clinically, a patient can complain about a discomfort/pain in the thigh or hip - that increases with load -days/weeks before fracture develops (or is diagnosed). Radiologically atypical fractures are characterized by a transverse or short oblique fracture line and are noncomminuted, while classical ST/DF osteoporotic fractures show a long oblique, longitudinal or sometimes spiral fracture configuration (126).
In a number of case-reports a thickening of the medial and lateral cortices of the femoral diaphysis and a localized periosteal reaction of the lateral cortex were described (126). Both these features however were not systematically observed and therefore they are currently not considered among major criteria for radiological definition and diagnosis of atypical ST/DF fractures, according to the ASBMR report recently published (125). Finally, a significant delay in fracture healing has been frequently described (126).
Even if these fractures have been mainly described as a complication of BP therapy, atypical fractures indistinguishable from those observed in patients treated with BP were found also in subjects with hypophosphatasia, in patients treated with corticosteroids or denosumab, or in subjects never exposed to BP (125-129).
Epidemiological data about prevalence and incidence of atypical ST/DF fractures in patients treated with BP are scarce and mostly derived from retrospective studies. The main limitation of these studies is related to the lack of an X-rays observation without a direct assessment of the radiological features of atypical fractures (short

oblique noncomminuted fracture configuration), which distinguish atypical ST/DF fractures from typical ones in elderly osteoporotic patients. Only the few studies in which the direct observation of X-rays allowed the ascertainment of radiological features of atypical fractures enabled us to define epidemiology and risk factors (130-141).

Atypical femoral fractures related to BP therapy seem to represent the 0.4-0.6% of all femoral fractures (131, 135). The incidence of atypical fractures in patients treated with BP is extremely variable from an estimate of 2 cases per 100,000 person-years to 113 cases per 100,000 person-years (132-141).

This high variability is related to a number of factors: the inclusion or not of ASBMR minor criteria (125) in radiological definition of atypical fracture (138, 142), the calendar year in which prevalence was estimated (137), and the duration of BP treatment (132, 134). In the general population (never treated with BP) the incidence of atypical ST/FD fractures is estimated from 0.3 to 2 cases per 100,000 person-years (133) with a high variability related to age (16 cases per 100,000 person-years in subjects aged >65).

Case-control studies published in the last 4-5 years evaluated the significance of the association between BP use and atypical ST/DF fractures and estimated the risk to develop an atypical ST/DF fracture during BP treatment. Most of these studies (130-132, 137, 138, 143-146) but one (136) confirmed an increased risk of atypical ST/DF fracture in patients treated with BP and pointed out that the risk increases with the duration of exposure to BP. One of these studies also showed that the BP discontinuation is associated to a risk reduction, even after a short time (132). Finally, two case-control studies identified other potential risk factors related to atypical femoral ST/DF fractures (130, 131) such as corticosteroids therapy, hypovitaminosis D, previous osteoporotic fractures, active rheumatoid arthritis.

The most likely hypothesis about pathogenesis of atypical femoral ST/DF fractures is represented by an excessive suppression of bone turnover in patients extremely susceptible to the antiresorptive effect of BP (125, 126, 147-150). This higher susceptibility could be related to intrinsic factors (vulnerable osteoclasts, reduced bone formation ability) or to external factors, most likely related to other drugs (corticosteroids, proton pump inhibitors) or diseases (rheumatoid arthritis, hypovitaminosis D). Even if this hypothesis is supported by the first studies investigating atypical ST/DF fractures pathology (149, 150), it was not confirmed in other studies who found in bone biopsies of patients with atypical ST/DF fractures and treated with BP a normal, not suppressed bone turnover (126).

No guidelines are available that define an evidence-based approach to prevent atypical femoral ST/DF BP-related fractures. On the contrary it has been clearly demonstrated that benefits derived from BP treatment are higher than potential risks (151). With the aim to minimize atypical fracture risk in patients subjected to long-term BP treatment, it has been proposed to consider some periods of *drug holiday*, after a thorough evaluation of the risk/benefit ratio and concomitantly with a correction/monitoring of other possible risk factors for atypical fractures (152-154).

Summary of evidences

The safety profile of BP is overall reassuring, also considering the long-term experience with these drugs and the lack of ascertained severe or life-threatening adverse events to date.

Acute phase response to amino-BP is limited to the first administrations, easy to prevent or manage and it does not seem to be associated with unwanted clinical consequences.

The availability of weekly or monthly oral formulations has improved the gastrointestinal tolerability and reduced the risk of side effects in this site, if the drug is taken correctly.

Intravenous BP use is not associated with a significant risk regarding renal function, provided an adequate hydration and when recommended doses and times of infusion

are respected. If indicated, their use is possible, eventually with a dose adjustment, even in patients with a mild impairment of renal function.
Other side effects are uncommon and, even if their presence should be looked at and excluded, they do not seem to overall compromise the risk/benefit balance of BP treatment.

Osteonecrosis of the jaw
It is widely accepted that the best way of management of ONJ is prevention, which is mainly based on risk factors control.
In patient who are starting a treatment with BP for OP, a dental evaluation with an eventual cleaning up before therapy is not necessary. Patients should be only advised to keep a good oral hygiene, as in general population, especially if their oral hygiene is not satisfactory.
When invasive dental procedures are required, starting BP treatment could be eventually delayed after dental problem is recovered, or alternatively dental procedures could be performed in the first 6 months of BP therapy.
In subjects who have been treated with BP for OP for less than 3 years and without individual risk factors (diabetes, immunosuppression, corticosteroids, smoking) the risk of ONJ during invasive surgical procedures is extremely low and no specific cautions or conducts are required.
Based on epidemiological data, the unwilling of the dentist to perform invasive dental procedures (such as tooth extraction) in patients treated with BP or considering dental procedures alternative to BP treatment, in the absence of other documented risk factors, seems to be not justifiable. Sometimes the lack of dental treatment itself could represent a risk factor for ONJ.
For subjects treated with BP for more than 3 years (with a compliance >80%) it is recommended to keep a regular professional oral hygiene, as suggested for the general population. If an invasive dental procedure (tooth extraction) is required, many guidelines suggest the drop off of BP for a 3 months period and the reintroduction of the drug after surgical wound is healed. There is no evidence that this approach actually reduces ONJ risk considering the persistency of drug effect for a long time. For the same reason however BP discontinuance for a brief time (1-2 months) likely does not compromise the efficacy of OP treatment.
Recently some authors proposed to stop the drug after tooth extraction until local mucosa is healed. Prolonged discontinuations of the drug should be arranged between both dentist and BP prescriber.
In cases of invasive dental procedures (tooth extraction), especially if individual risk factors are present (diabetes, immunosuppression, corticosteroids, smoking, alcohol consumption) an adequate antibiotic prophylaxis is suggested (amoxicillin eventually combined to metronidazole, to be started a few days (2 to 5) before dental procedure and to be continued for at least 10-15 days after, until gingival mucosa healing). Antibiotic prophylaxis should be combined with a surgical procedure involving primary closure of the site of extraction with mucoperiosteal flaps.
There is no contraindication to perform dental implantations during BP treatment. In the literature only 12 cases of ONJ associated to implantation have been reported, with an estimate of risk of implant loss of 0.88%. However a possible complication of implantation itself is perimplantitis, which can increase ONJ risk during BP treatment. It is therefore advisable that the patient complies with a strict oral hygiene program.

Atypical femoral fractures
Atypical femoral subtrochanteric/diaphyseal fractures are an uncommon complication of a prolonged exposure to BP, which however have been described also in patients never exposed to BP.
Based on available data, the risk/benefit balance of BP treatment in osteoporosis prevention clearly favors benefits.
With the aim to minimize atypical fracture risk in patients treated with BP it should be suggested to:
- consider some periods of *drug holiday* after a thorough evaluation of the risk/benefit balance;

- correct/monitor other possible risk factors for atypical fractures.

STRONTIUM RANELATE

Common side effects of strontium ranelate therapy are usually mild and transient. The most frequent side effects are nausea and diarrhea, which usually develop at the beginning of the treatment and tend to disappear after 3 months of therapy.

The hypothesis of an increased vascular risk came from a combined analysis of registration trials that showed in 5 years an increased annual incidence of venous thromboembolism in subjects treated compared to placebo (0.9% *vs* 0.6%; RR 1.4; 95% CI: 1.0-2.0) (155).

A retrospective study on the United Kingdom General Practice Research Database (GPRD) (156) showed that women with OP have a higher risk of venous tromboembolism compared to women without OP, regardless of the treatment (no therapy, strontium ranelate, alendronate). Similar results were reported in other studies (157,158).

Recently a large prospective European study with a 3-year follow-up was published, that included 32,446 women among whom 12,046 were treated with strontium ranelate (159). The incidence of venous thromboembolism was 2.1 per 1,000 person-years, and 3 per 1,000 person-years in the subpopulation aged >80. It was therefore established that the drug was contraindicated in patients with previous or current venous thromboembolism and in cases of temporary or permanent immobilization. The opportunity to maintain the treatment in patients aged >80 and at risk of venous thromboembolism was deemed worthy to be reassessed (160).

Strontium ranelate administration has been associated with rare cases of severe allergic skin reactions, sometimes with systemic symptoms potentially fatal in the contest of Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome or of the Stevens-Johnson syndrome (toxic epidermal necrolysis) (161-164).

The pathogenesis of these hypersensitivity syndromes is not clear since strontium is an element present in nature in human organisms and ranelate is poorly absorbed. Postmarketing experience on treated patients reports a number of cases lower than 20 per 570,000 person-years of exposure and this low incidence of reactions is probably the reason why no cases have been reported in clinical trials.

Even in the European observational study on more than 12,000 patients no skin reactions were recorded (159). In conclusion, strontium ranelate causes few non-skeletal effects both concerning vascular events and hypersensitivity reactions (165). However, considering the eventuality that these events may occur, in cases of skin reactions in the first 2 months of treatment drug needs to be stopped and not reintroduced (160).

Recently the Pharmacovigilance Risk Assessment Committee (PRAC), a European Medicines Agency (EMA) organism responsible for the safety evaluation and monitoring of human drugs, pointed out a possible association between the use of strontium ranelate and an increase of heart side effects, above all myocardial infarction. PRAC reanalyzed cardiac side effects in 7 studies on postmenopausal OP (3803 patients treated with strontium ranelate), 1 study on male OP (173 treated patients) and 2 studies on osteoarthritis (586 treated patients). In a pooled analysis of the studies on postmenopausal OP (7572 patients) an increased number of myocardial infarctions was observed in patients treated with strontium ranelate compared to placebo (1.7% *vs* 1.1%, OR: 1.6; 95% CI: 1.06-2.38), even if no differences in cardiovascular mortality and total mortality between the two groups were found. From studies on male OP and osteoarthritis, due to the small sample size and to the low frequency of events, no conclusions could be drawn. However it should be reported that in a post-marketing evaluation of 3,402,769 person-years, from September 2004 to February 2013, no alarming signals of heart diseases were observed. Also in the aforementioned European observational

study no cases of heart diseases related to therapy were reported and the observed incidence of myocardial infarction was 1.3 per 1000 person-years, lower than in clinical trials (159).
Regarding the possible pathogenesis of cardiac damage, some hypotheses have been proposed about the relationship between the calcium-like effect of strontium ranelate and ischemic heart disease and a possible effect on hemostasis, but these hypotheses still need to be demonstrated.
Based on studies to date considered, on April 25, 2013, the EMA's Committee for Medicinal Product for Human Use (CHMP) received PRAC observations and recommended that strontium ranelate should only be used for the treatment of severe OP in postmenopausal women at high risk for fracture and severe OP in men at increased risk for fracture (166). On this basis, the Italian Medicines Agency (AIFA) recently modified the prescription modalities of this drug, stating that it has to be prescribed only by a physician skilled in OP treatment and after filling out a therapy certification. Moreover, the treatment with strontium ranelate is contraindicated in patients with a history of thrombosis or thromboembolism, cardiovascular disease, cerebrovascular disease, or peripheral vascular disease. The same restrictions have to be applied to subjects at high risk for thrombosis or cardiovascular events, even in absence of a history of these events (167).

Summary of evidences
Strontium ranelate should be immediately interrupted in cases of skin reactions in the first months of treatment.
Strontium ranelate should not be prescribed to patients with:
- previous or current venous thromboembolism;
- temporary or permanent immobilization;
- uncontrolled hypertension and/or ischemic heart disease, obliterating arteriopathy of the lower limbs, and cerebrovascular diseases.

The treatment is also contraindicated in patients without a history of cardiovascular events, but with risk factors for them (hypertension, hyperlipidemia, diabetes, smoking).

SELECTIVE ESTROGEN RECEPTOR MODULATORS

Problems related to side effects of hormone replacement therapy (HRT) (168) stimulated pharmacological research to develop molecules that could keep the benefits of estrogen therapy reducing the incidence of adverse events, which are still contraindicating HRT for the prevention and treatment of postmenopausal OP and related fractures.
Major concerns regarding the founder of the class, raloxifene, which was introduced on the market in the second half of the 90s specifically indicated for postmenopausal OP prevention and treatment, are related to an increased risk of thrombotic and thromboembolic events associated to the treatment.
This association, already observed in the registration trial, is expressed by a RR of 3.1 (95% CI: 1.5-6.2) for venous thrombosis and of 4.5 (1.1-19.5) for pulmonary thromboembolism (169). The incidence of these side effects is higher in the first 2 years of treatment, when the RR is higher than 6 (6.6; 95% CI 0.95-50.4), then progressively decreases in the following years (170). Overall the size of this side effect is approximately comparable to what is observed during HRT (171). The importance of this result needs also to be considered in the context of inclusion criteria of these studies, which excluded subjects with previous thromboembolic events. Moreover, as following studies confirmed, specific predisposing factors to these side effects cannot be identified (172). Finally, the causal relationship between raloxifene and thrombotic and thromboembolic events was confirmed by a meta-analysis of 9 studies including more than 24,000 patients, which showed a total increase of venous thrombosis and thromboembolism of 62% (OR 1.62; 1.25-2.09) (172).
Considering other possible side effects, in the RUTH study on 10,000 women with

coronary heart disease or with risk factors for coronary heart disease and treated for more than 5 years with raloxifene, besides an increase of the incidence of thrombotic and thromboembolic events, there was a significant increase of deaths from stroke in subjects treated with raloxifene (hazard ratio 1.49; 95% CI: 1.00-2.24), while the total number of strokes (fatal and not) was comparable to healthy subjects in the placebo group (173).

Further studies on the same population found that smoking was a risk factor for this side effect (174) and that a concomitant therapy with acetylsalicylic acid or other antiplatelet agents could not reduce the incidence of thrombotic and thromboembolic events (175). Even if the association between raloxifene and thromboembolic diseases was confirmed by all the studies on this issue, the employment of a composite assessment score which includes all the possible outcomes of HRT demonstrated that raloxifene shows an overall positive risk/benefit balance with a higher survival rate of treated patients compared to control population (176).

Finally, it should be noted that raloxifene is associated with other side effects which are clinically less relevant but still responsible for a higher discontinuation rate compared to placebo (177), such as leg cramps and a worsening of postmenopausal vasomotor instability (178). Therefore the overall data suggest that raloxifene should not be prescribed to subjects with previous thrombotic events and similarly it should be immediately stopped in subjects at higher risk for these events (prolonged immobilization). Also in patients with previous cerebrovascular events the drug should be used with caution.

Bazedoxifene, another selective estrogen receptor modulators (SERMs) recently introduced on the market, has not yet been investigated in long-term post-marketing observational studies in which the incidence of side effects in the general population can be assessed. Considering the possible side effects, from registration trials the safety profile of bazedoxifene seems to be similar to that of raloxifene regarding the incidence of thromboembolic diseases, leg cramps and vasomotor instability (179, 180). Also in this case a higher incidence of thromboembolic disease was observed in a population of postmenopausal women from whom subjects with previous thrombotic or thromboembolic events were excluded. In the extension studies at 5 (181) and 7 (182) years, bazedoxifene showed similar results to those observed in the first 3 years of treatment, with a higher incidence of thrombotic and thromboembolic events, vasomotor disturbances and leg cramps than in the placebo group.

Summary of evidences

Even if the overall effect on mortality prevention seems to be positive, SERMs cause an increased risk of thromboembolic events, especially in the first 2 years of treatment. On this basis, this drug should not be prescribed and the treatment should be stopped in situations of increased risk (*i.e.* prolonged immobility, bedridden patients). The concomitant therapy with antiplatelets agents does not seem to reduce the risk of thromboembolic events. Raloxifene also seems to increase the risk of stroke, especially in subjects at higher risk (older age, hypertension, diabetes, previous cardiovascular diseases, smoking, atrial fibrillation, left ventricular hypertrophy).

Bazedoxifene shows a safety profile very similar to that of raloxifene.

SERMs can induce a worsening of postmenopausal symptoms (leg cramps, vasomotor disturbances) especially at the beginning of the treatment.

■ DENOSUMAB

Notwithstanding the limitations related to its recent introduction on the market, all the published studies seem to allay fears of possible extra-skeletal effects of denosumab (Dmab), due to a theoretical interference with immune response and inflammation.

No reliable data demonstrating an increased incidence of neoplasms and infectious diseases in patients treated with this drug are available.