Paget's disease

I. Bertoldi, L. Cantarini, G. Filippou, B. Frediani

Centro per l'Osteoporosi e la Diagnosi Strumentale OsteoArticolare, Sezione di Reumatologia, Università di Siena, Italy

SUMMARY

Paget's disease of bone is the most common metabolic bone disease after osteoporosis and affects 2-4% of adults over 55 years of age. Its etiology is only partly understood and includes both genetic and environmental factors. The disease may be asymptomatic and can be uncovered incidentally on x-ray or in biochemical tests performed for another condition. It can also manifest itself with bone pain, deformity, fracture or other complications. Paget's disease is diagnosed by x-rays and in general has very typical radiological features, but occasionally the clinical picture may be unusual and a differential diagnosis of sclerotic or lytic metastases needs to be considered. Plasma total alkaline phosphatase activity is the most clinically useful indicator of disease activity. It is elevated in most untreated patients, but may be within the normal range in patients with monostotic or limited disease. Bisphosphonate therapy is indicated for patients with symptoms and should also be considered in patients with disease sites that suggest a risk of complications, such as long bones, vertebrae or base of the skull. Orthopedic surgery in Paget's disease patients includes almost exclusively the correction of fractures and arthroplasty.

Key words: *Paget, Bone remodeling, Pathogenesis, Therapy.*

Reumatismo, 2014; 66 (2): 171-183

DEFINITION, CLINICAL PRESENTATION AND EPIDEMIOLOGY

Paget's disease is named after Sir James Paget, who first described this pathology in 1877 (1). This disorder consists of a focal alteration of bone remodeling with two main pathological hallmarks: the structural integrity of the bone or its biomechanical efficiency is no longer maintained and progression occurs at an extremely swift and haphazard pace. This process is protracted over time, spreads and translates into weakness, deformity, increased fracture risk and pain in the involved bone segment. The deformity of the affected areas alters weight distribution, with a consequent increased risk of secondary arthritis. The increased volume of affected areas may result in the compression of nerve structures, whenever the skull or the spinal column is involved (Tab. I). The most typical form of this radiculitis impacts the acoustic nerve, with secondary hearing loss. The Paget's bone is much more vascularized than normal bone, thus leading to potential localized pain (2). However the disease may be diagnosed in an asymptomatic patient in a blood test that reveals elevated levels of alkaline phosphatase, or in an x-ray.

Paget's disease mainly affects the axial skeleton, in particular the lumbar-sacral sector, pelvis, skull, femur and tibia (3). The presence of a high number of asymptomatic patients has made it difficult to carry out epidemiological studies on this disease. Various data from a combination of multiple studies, including reviews of abdominal x-rays, autopsies, questionnaires and serum alkaline phosphatase tests (4-7), reveal an incidence of around 1-3% in over 50s, and 8% in over 80s,

Table I - Clinical presentation of Paget disease of bone.

Incidental finding on an x-ray or in biochemical test
Bone pain
Arthopathy
Deformity
Fracture
Hearing loss
Neurological complications
Osteosarcoma

Corresponding author:
Ilaria Bertoldi
Centro per l'Osteoporosi
e la Diagnosi Strumentale OsteoArticolare
Sezione di Reumatologia
Università di Siena, Italy
E-mail: bertoldilaria@gmail.com

at least in some countries (8). The geographic distribution is definitely peculiar, because this pathology is extremely rare in the non-Caucasian population, while among Caucasians it is mostly widespread in England. A few studies have also reported a higher incidence of this disease in rural areas, and in particular in subjects who have frequent contacts with animals (9). Prevalence increases exponentially with age, approaching 30% among over 85 years. The prevalence of Paget's disease in the United Kingdom (UK) has shown a rapid decline and has been recently estimated at 2% among over 55 years (10, 11). This suggests that environmental factors may play a role in the development of this condition. The incidence in the UK is currently similar to that of Caucasian populations in other countries. In Italy, a recent prevalence study (12) has been conducted in the cities of Turin and Siena on the basis of x-ray, scintigraphy and biochemical tests. Among over 60 years of age, the overall incidence of the disease accounts for just over 1% and is greater among males with no significant differences between the two cities. It has also shown an increase with age (from 0.7% to 2.4% over several decades), but no significant differences compared to previous studies conducted in Italy. An unexpected greater severity of the disease has been observed both in the sporadic and familial forms in the Campania region (13).

PATHOGENESIS: GENETIC AND ENVIRONMENTAL FACTORS

The variable prevalence of Paget's disease in different geographies and its familial form suggest a role of both genetic and environmental factors. In 2002, in Canada, Laurin et al. found a mutation in the *SQSTM1* gene in almost 50% of individuals with the familial form and in 16% of those with the sporadic form (14). Later, in the United Kingdom, Hocking et al. have found the same mutation in 19% of cases of familial Paget's disease and in 9% of sporadic cases (15). Subsequently investigators have highlighted that the same mutation is often present on a conserved haplotype, which is consistent with a stable genetic change occurred in the affected population (16). This observation of a *founder effect* perfectly matches the epidemiology of Paget's disease (17), but only in the case of the SQSTM1 mutation. In Europe, Australia, and the United States, comparable rates of SQSTM1 mutation have been reported in or around the ubiquitin-associated domain. There are several specific mutations, the most common of which is, a proline-to-leucine substitution at aminoacid 392 (P392L). Scientists have tried to correlate the severity of the disease with the genotype, but the results have been inconsistent (18-21). Attention was therefore shifted to the role of p62 (a product of the *SQSTM1* gene) in signaling osteoclast activation via the nuclear factor kappa B. Since this initial discovery, polymorphisms in the genes affecting osteoclast maturation, activation, and fusion pathways have shown to predispose to Paget's disease. Examples (22):

- TNFRSF11A, which codes for the receptor activator of nuclear factor (RANK) kappa B;
- TNFRSF11B, which codes for osteoprotegerin;
- CSF1, which codes for the macrophage colony-stimulating factor 1;
- OPTN, which codes for optineurin, a member of the nuclear factor kappa B modulating protein family.

Although there is some evidence that measles and canine distemper viruses can infect osteoclasts and modify their phenotype, there is not enough evidence confirming that these infections by themselves can cause Paget's disease (23-25). Multiple epidemiologic studies from around the world have failed to identify conclusively any triggering environmental factors that can actually predispose to Paget's disease, although many have been proposed, such as a rural setting, trauma, infection, and milk ingestion (26-28). It is also possible that some local changes resulting from bone and marrow aging may favor the development of this disease. In fact the main risk

factor for Paget's disease is perhaps aging, followed by family history. To date genetics cannot fully account for the development of this disease, since there are cases of individuals with *SQSTM1* mutations who have no clinical symptoms, not even at an older age, and patients with Paget's disease who have no *SQSTM1* mutation (20, 29).

COMPLICATIONS

Paget's disease is the second most common disorder of the aging bone after osteoporosis. However, unlike osteoporosis, which presents as a systemic fragility of bone, the clinical manifestations of Paget's disease depend on which bones are affected and how enlarged or misshapen they have become.

Common complications

As a consequence of the abnormal bone remodeling, many patients present with bone pain. Bone deformity, headache, and hearing loss may frequently occur, as well as fractures and nerve compression syndromes (such as spinal stenosis, sciatica, cauda equina syndrome). The *pagetic* bone may not necessarily be the source of pain, which instead could be caused by degenerative changes at affected sites (30, 31).

Metabolic complications

Metabolic complications are rare today, but they can occur in elderly patients who have an active polyostotic (multibone) disease (32). The accelerated rate of bone remodeling and the increased vascularity of the pagetic bone have been reported to cause high-output heart failure. In theory, treatment should aim at slowing down the blood flow in the pagetic bone and restoring the bone turnover to more normal levels (33). Hypercalcemia can occur, when patients with Paget's disease are immobilized for any reason. Also a higher incidence of kidney stones has been identified in these patients (34, 35).

Osteosarcoma

Osteosarcoma rarely arises in the pagetic bone. Yet Paget's disease may account for a significant number of cases of this cancer in the elderly (36). In these cases, osteosarcoma is expected to derive from a second genetic mutation, therefore it can be distinguished from the form occurring in young patients and is poorly responsive to treatment (37). In Scandinavia and Japan, where Paget's disease is rare, the second peak of age-correlated osteosarcoma shows the same mutation (38, 39). This cancer presents with pain, soft-tissue swelling, and variable elevations in serum alkaline phosphatase.

Investigations to date suggest that pagetic lesions and osteosarcomas arising in pagetic bone are probably both caused to some extent by an overexpression of the RANK ligand by stromal cells and may not be related to an inherent defect of osteoclasts (40).

Giant-cell bone tumors

Giant-cell tumors are also rare, but they can arise in the pagetic bone. A cluster of cases was reported in Avellino and other towns of southern Italy (13). Furthermore the lesions occur in older individuals and in different sites compared to those seen in the benign giant-cell tumors affecting patients without Paget's disease.

Metastases

Typical bone metastases associated with lymphomas, prostate cancer, and breast cancer hardly ever occur in pagetic sites (41). A recent case study has noted that patients with prostate cancer and Paget's disease had a later onset of metastasis in the bone than patients without concomitant Paget's disease (42).

The assessment of a patient with Paget's disease requires a comprehensive understanding of potential musculoskeletal consequences at an older age. Pain in Paget's disease is often multifactorial. In the elderly, all causes need to be considered, including end-stage degenerative diseases of the spine, hip, and knees, mechanical instability, compression fractures of the spine, and neuropathies. Therefore, a thorough clinical evaluation is required to plan an adequate treatment strategy.

IMAGING

A plain radiography of the affected bones outlines the anatomy of the problem and gives some insights into the cause of pain. Computed tomography or magnetic resonance imaging may prove useful in cases of spinal stenosis, cauda equina syndrome, compression fractures, or suspected malignancy, but they are expensive and not always necessary.

Radiographic features

Paget's disease is presumably a disease of the osteoclast, and the earliest visible lesions are described as lytic. Nevertheless it is unusual to see a purely lytic lesion, which can only be found in the skull (*osteoporosis circumscripta*), the femur or the tibia with an advancing edge of pure osteolysis. It more often manifests itself with areas of resorption by osteoclasts and areas of bone formation by osteoblasts, thus reflecting the combination of both processes in this disease. Radiographic findings on plain films are usually conclusive, when they show an enlargement of the affected bone, deformity, coarsened trabeculae, and thickened cortices with tunneling (43). In weight-bearing bones, pseudo-fractures may appear on the convex surface. These bone incongruities may persist for years, heralding fracture only when there is focal pain (44).

Bone scintigraphy

It is more sensitive than plain radiology in detecting pagetic lesions, and is mainly indicated in newly diagnosed patients to determine the distribution of the disease. It makes it possible to identify the involved bones (important at baseline) with potential complications, depending on the sites, such as the skull base, the spine and long bones.

Biopsy

If such diagnostic findings are not present on the x-ray, then bone biopsy is indicated. In the United States and Canada, where Paget's disease is fairly common, biopsy is rarely used and generally reserved for cases in which the differential diagnosis may point to a potential bone cancer or when the cortex is not visible, the lesions have an unusual pattern or location, or there is a single sclerotic vertebral body (45). Another indication for biopsy is a *new* pagetic lesion. For unknown reasons, the pattern of skeletal involvement in Paget's disease tends to be stable throughout the life of the patient. This is another reason why a baseline skeletal scintigraphy (or alternatively a bone scan) is required.

BIOCHEMICAL MARKERS

A serum alkaline phosphatase (ALP) screening test is usually sufficient to measure bone turnover. Alkaline phosphatase is produced by osteoblasts and is a marker of bone formation, despite its limited accuracy. It is often elevated in active Paget's disease (46), but many patients may have normal serum ALP levels, particularly if they have the monostotic (single-bone) disease. The measurement of other bone formation markers, such as bone-specific alkaline phosphatase, osteocalcin, and procollagen type I peptides, and of bone resorption markers, including the pyridinolines, hydroxyproline, and cross-linked collagens, do not offer any additional information to the serum ALP level (47, 48). Therefore, since the ALP test is rather inexpensive, available, and reliable, it should be considered the marker of choice in combination with the assessment of liver function by gamma-glutamyl transpeptidate or 5´nucleotidase test to exclude that its increase is to be associated with the liver rather than the bone (49).

MEDICAL TREATMENT

Medical treatment of Paget's disease aims to normalize or at least reduce as much as possible abnormal bone turnover. This objective has become achievable with the advent first of calcitonin and later of bisphosphonates. The indications for treatment of Paget disease of bone are indicated in Table II.

Table II - Indications for treatment of Paget disease of bone.

Pain in pagetic bones
Neurological complications
Significant osteolytic lesions
Involvement of long bones, vertebrae or base of skull
Before surgery involving pagetic bones
Significant joint involvement (e.g. hip joint)

TREATMENT WITH BISPHOSPHONATES

Virtually all clinically-developed bisphosphonates have been tested in Paget's disease patients. On the basis of their availability in Italy and their approval for the treatment of Paget's disease, they can be classified as follows (2):

1) drugs with an indication for Paget's disease, but unavailable in Italy: alendronate 40 mg/die, tiludronate, olpadronate, oral pamidronate;
2) drugs *not approved* for Paget's disease, but widely used in Italy on an *off-label* basis: clodronate intravenously (IV), pamidronate IV;
3) drugs *approved* and available in Italy: oral etidronate, oral risedronate, neridronate EV, zoledronate IV.

Efficacy criteria

A comparison of efficacy among the various available therapies is complicated by the lack of standardized assessment criteria or specific reporting standards [*e.g.* Committee for Proprietary Medicinal Products (CPMP) or Food and Drug Administration (FDA)]. In most clinical trials, the main objective is the reduction of ALP. Other objectives (pain relief, improved quality of life, prevention of complications) are mainly secondary end-points, therefore very large samples and long-term studies would be required to achieve statistically-significant variations. In general the following aspects are evaluated:

- percentage drop in ALP. A variation of this efficacy evaluation method considers a drop in ALP beyond normal levels (reduction of excess ALP);
- percentage of patients with ALP reduction greater than 50% or 75%. This method has the same limitations as the previous one, but it offers the advantage of providing an estimate of patients responsive to the therapy (responders), albeit based on an arbitrary criterion;
- percentage of ALP normalization. It was not used in the past due to the limited efficacy of available treatments. The comparison between various treatments in non-head-to-head studies is not very reliable and requires a substantial equivalence in terms of disease severity among the patients included in the various trials;
- for all of the above criteria, it is also necessary to ensure equivalence between treatments administered to patients who have already received a bisphosphonate treatment in the past.

Etidronate

Etidronate was the first bisphosphonate utilized to treat Paget's disease. The suggested doses are 5-20 mg/kg/die, which bring about reductions in ALP between 40 and 70% (50, 51) along with relief of symptoms. The higher doses offer a better control of the disease, but are associated with more significant side effects in terms of gastrointestinal disorders (52) and, above all, bone mineralization deficiencies (53) with an increased risk of fractures (54).
Hence it is recommended not to exceed a dose of 400 mg/die for no more than 6 months. This regimen often fails to bring about bio-humoral remission in patients with very active Paget's disease (55). Etidronate, along with subcutaneous calcitonin, were the only drugs approved in Italy for treatment of Paget's until 2006, when neridronate and zoledronate were also approved.

Pamidronate

Pamidronate was initially utilized in an oral formulation (56-59), which proved to be poorly tolerated. The drug's availability in the intravenous form for the treatment of malignant bone complications has led to a variety of regimens (60-68). The most-utilized protocol (*off label* in most countries)

is 3-6 intravenous infusions of 60 mg of pamidronate (over 3-21 days). This dosage leads to a 50-80% reduction of ALP, a significant relief of symptoms (57-59), and occasionally also an improvement in radiological (69, 70) or scintigraphic (71, 72) patterns. Its efficacy lasts for fairly prolonged periods after a single cycle of treatment considering the extent of turnover suppression achieved. In general, the greater the suppression, possibly within the normal range, the longer the efficacy (73). The improvement of symptoms can also include the remission of neurological complications (33, 74, 75).

Like other amino-bisphosphonates administered intravenously, the treatment with pamidronate may be associated with an acute phase reaction (fever, muscular pain) lasting 1-4 days, especially after the first infusion, as well as various types of mucositis (76). The use of pamidronate over the long-term at medium-high doses cause modest bone mineralization deficiencies of uncertain clinical significance (77, 78).

Tiludronate

Tiludronate is a first-generation bisphosphonate (which does not include a nitrogen group but a sulphydryl group). It is approved in several European countries, but it is not available in Italy. At the recommended dosage of 400 mg/die p.o. for 3 months, it leads to a significant 40-70% reduction of ALP (79, 80). Tiludronate is not associated with the esophageal problems caused by amino-bisphosphonates, but it can cause mild diarrhea.

Risedronate

Residronate is an amino-bisphosphonate developed for the treatment of Paget's disease with an oral formulation. In a phase 2 trial (81) a dosage of 30 mg/die p.o. for 2 months has been compared with etidronate 400 mg/die. Risedronate was able to normalize ALP in 75% of cases compared to 15% of patients on etidronate (82). A biohumoral improvement has been associated with an improvement of the symptoms and the radiological picture. After these studies, Risedronate has been approved in Italy for Paget's disease treatment, but it has never been included in the national reimbursement drug list.

Clodronate

Clodronate is a first-generation bisphosphonate approved in Italy for the treatment of osteoporosis and malignant bone complications, but not for the treatment of Paget's disease. However clodronate has been the most widely used drug off label for this disease in recent years in Italy. The drug has been the object of a few *spontaneous* studies (83-86). The most frequently used dosage is 300 mg in 500 cc of saline solution for 5-12 days depending on the severity of the disease. This dosage leads approximately to a 50-70% reduction in ALP.

Alendronate

Alendronate at a dosage of 40 mg/die for 6 months has proven efficacious in reducing disease activity and improving the radiographic picture both in studies comparing it against etidronate and in non-controlled studies (87-90). Alendronate is not available in Italy in the formulation approved for the treatment of Paget's disease.

Ibandronate

Ibandronate has been studied at a dosage of 2 mg (single infusion) to be repeated if necessary at higher doses in case of failure or rapid relapse (91). This drug is not approved for the treatment of Paget's disease, but it is available on the Italian market.

Olpadronate

Olpadronate (chemically very similar to pamidronate) is only available in some countries and has been the object of some non-approval-oriented studies. It has yielded similar results to pamidronate (92, 93).

Neridronate

Neridronate is an amino-bisphosphonate with an intermediate chemical structure in between alendronate and pamidronate. It is available in Italy only in the parenteral formulation. Up to 25 mg can also be administered intramuscularly. The maximum approved daily dosage is 100 mg in 500 cc

of saline solution. After an initial approval for the treatment of imperfect osteogenesis in both adults and children, the drug was approved (and covered by the national healthcare service in the H2 category) in early 2006 with an indication for the treatment of Paget's disease. Other studies have been published (94), including one phase 2 study (95), which has reported a dose-effect curve that remains linear up to a maximum dosage of 100 mg x 2 intravenously.

Zoledronate

Zoledronate is a nitrogen-containing bisphosphonate. It is administered as a single infusion over 15 min. A re-treatment is often unnecessary for years. In 2005 a randomized clinical trial has demonstrated the efficacy of zoledronic acid 5 mg intravenously compared with oral risedronate for the treatment of Paget's disease (96). In observational extension studies which lasted for as long as 6.5 years, zoledronic acid has shown to be superior to risedronate in terms of number of patients experiencing a sustained clinical remission (97). Although there are currently many bisphosphonates available on the market, a single infusion of 5 mg of zoledronic acid seems an ideal treatment at least in patients who have a contraindication or an aversion to intravenous therapy. This drug tends to normalize the serum ALP level quickly over the long term, also in patients who have used other bisphosphonates in the past or has become resistant to them. This has led to the approval of a dose of zoledronate 5 mg (Aclasta) for the treatment of Paget's disease by both the FDA and the European Medicines Evaluation Agency (EMEA).

Bisphosphonates reduce bone turnover but do not correct deformities

In randomized clinical trials, bisphosphonates have shown to restore bone remodeling to more normal levels, relieve bone pain, lower the serum ALP level and heal radiographically-visible lesions, but they have not been able to prevent the progression of deformity or restore the structural integrity of the bone.

A study named *Paget's Disease: Randomized Trial of Intensive Versus Symptomatic Management* (PRISM) conducted on a sample of 1324 patients with Paget's disease in the United Kingdom has shown no difference in the incidence of fracture, orthopedic surgery, quality of life, or hearing loss. This study has foreseen a follow up at 2 and 5 years and has compared bisphosphonate treatment versus symptomatic management. However a statistically significant difference has been detected in serum ALP between the two groups (P<0.001) (98). In an observational extension study of zoledronic acid (97) ¾ of fractures occurred in the group treated with zoledronic acid, thus confirming the findings of the PRISM study.

CALCITONIN

Calcitonin can still be useful in easing pain in Paget's disease, healing bone lesions, and reducing the metabolic activity of the pagetic bone in patients who cannot receive bisphosphonates. It is administered by injection at doses of 50 to 100 IU daily or every other day. Although it may not offer a protracted clinical remission, it remains a safe, well-tolerated, and well-studied drug for the treatment of Paget's disease and is approved for this indication (99, 100).

DENOSUMAB

This drug has not been formally studied in Paget's disease, but recent case reports have shown it can be effective in patients affected by this disease (101).

SURGERY

Orthopedic surgery in Paget's disease patients almost exclusively consists in the correction of fractures and arthroplasty. Any surgery in a segment of pagetic bone is almost always complicated by greater than normal bleeding (102). Medical treatment may reduce this complication (103),

although results are still controversial. An accidental fracture of a segment of a pagetic bone is often complicated by slow consolidation and poor alignment (104, 105). There are no studies that show improved results in terms of the healing with an immediate treatment with bisphosphonates after surgery. The surgical approach may be necessary in cases of symptomatic bone deformity, especially if complicated by Looser fractures. In these cases, osteotomy must be preceded by an intensive treatment with bisphosphonates, preferably external fixators (106). There is only some anecdotal evidence of improvement of Looser fractures with medical bisphosphonate therapy. Patients with severe arthritis, especially in the hip and knee, can also be treated with prostheses. However this operation can often be complicated by ectopic calcifications and poor integration with the bone tissue (107).

MONITORING OF SPECIFIC DRUG TREATMENT

The management of Paget's disease is depicted in Table III. The goal of Paget's disease treatment must be the regression of symptoms along with the improvement of the radiological picture. However, as most patients begin treatment when the disease is at an advanced stage, prevention of complications becomes the main priority. For this purpose it is necessary to keep the disease in a state of remission or limited activity, therefore therapeutic monitoring must be based on bone turnover assessment. With regards in particular to fast-acting drugs, bone re-absorption markers decrease significantly within just a few days. Total ALP is the most widely utilized bone turnover marker in the clinical practice, as its levels correlate well with the extent and activity of the disease, and also has a very good variation coefficient (<10%). The level of the bone specific enzyme is certainly more accurate for patients with a concomitant liver disease, and is probably also more sensitive in cases of limited monostotic Paget's disease. A follow-up scintigraphy is almost never justified, both because it offers no substantial advantages over ALP measurement and it involves exposure to radiation. A second bone scintigraphy may be useful to check the evolution of the disease with a small monostotic symptomatic lesion and normal ALP levels.

Table III - Management of Paget disease.

Presentation	**Bone pain or deformities**	**↑ALP**	**Rx alterations**
First level exams	**Plain radiography**	**Scintigraphy**	
	if Paget	*if positive*	
	Scintigraphy ALP	Plain radiography of affected bone	ALP
	Uncertain Rx		
Second level exams	MRI - CT - Others		
	Uncertain diagnosis		
Third level exams	Bone biopsy		
Treatment	*If active disease*		
	Bisphosphonate		
Follow-up	ALP assessment after 6 month		
	↓≥25%		↓<25%
	Relapse: ↑ALP ≥25% of normal value (upper limit) or Reduction ALP <50%		
	Re-treatment Higher dosage of Bps other Bps		

ALP, alkaline phosphatase; Rx, x-ray; MRI, magnetic resonance imaging; CT, computed tomography; Bps, bisphosphonates.

In the monitoring of bisphosphonate therapy, the following items should be kept into account (2):

1) When utilizing total or bone ALP for monitoring purposes, it should be remembered that the nadir is reached after no less than 6 months from the beginning of treatment. An ALP measurement prior to 6 months is not justified, as it cannot provide any indication as to the efficacy of the treatment cycle.
2) The drop in ALP after re-treatment with bisphosphonates is almost always lower to that attained during the first treatment cycle.
3) There are forms of Paget's disease that are extremely limited or localized in critical areas (peri-articular areas, skull, vertebrae) and therefore symptomatic which may be associated with normal ALP levels. In these cases, the re-treatment threshold may be identified within the normal range based on some individualized clinical criteria.
4) There is data, recently supported by the follow-up results Zoledronate study (97), which confirms that the complete normalization of ALP in subjects with moderate-severe forms of Paget's is associated with a very long-term, possibly permanent, suppression of the disease, thus leading to a clinical picture with inactive disease. Such outcome is occasionally found in very elderly subjects, whose only indication of the prior disease is the persistence of radiographically visible lesions.
5) Indications for re-treatment. There is no consensus regarding a definition of relapse requiring a new cycle of treatment. An increase in ALP after it reaches its nadir at 6 months after the beginning of treatment is physiological, even when normalization of bone turnover has not been attained. In fact, it should be remembered that intensive and protracted cycles of treatment bring about a suppression of the turnover even of normal bone tissue, which may contribute to classify incorrectly a patient with small lesions as being in complete remission. A few months after the treatment cycle, there are inevitably signs of a gradual restoration of the turnover of the non-pagetic bone. However, a reactivation of the disease may be considered only when this increase exceeds 25%. In the case of acquired resistance to a drug, *i.e.* when at 6 months from the administration of treatment, suppression of ALP is below 50% of baseline values, it is useful to switch to another bisphosphonate (108, 109).
6) Young subjects. The detection of pagetic lesions in young subjects, especially females, may raise uncertainties with regard to possible teratogenous risks or long-term safety. The almost inevitable evolution of the disease over the years requires an adequate medical treatment. Although experimental studies seem to exclude any teratogenicity of the bisphosphonates, it is reasonable to advise postponing a pregnancy for a few months after a treatment cycle with bisphosphonates.

REFERENCES

1. Paget J. On a form of chronic inflammation of bones (osteitis deformans). Med Chir Trans. 1877; 60: 37-64.
2. Adami S, Bartolozzi P, Brandi ML, Falchetti A, Filipponi P, Gonnelli S, et al. Linee guida per la diagnosi e la terapia del Paget's disease. Reumatismo. 2007; 59: 153-68.
3. Guyer PB, Chamberlain AT, Ackery DM, Rolfe EB. The anatomic distribution of osteitis deformans. Clin Orthop Relat Res. 1981; 156: 141-4.
4. Tiegs RD, Lohse CM, Wollan PC, Melton LJ. Long-term trends in the incidence of Paget's disease of bone. Bone. 2000; 27: 423-7.
5. Altman RD, Bloch DA, Hochberg MC, Murphy WA. Prevalence of pelvic Paget's disease of bone in the United States. J Bone Miner Res. 2000; 15: 461-5.
6. Barker DJ. The epidemiology of Paget's disease of bone. Br Med Bull. 1984; 40: 396-400.
7. Detheridge FM, Guyer PB, Barker DJ. European distribution of Paget's disease of bone. Br Med J (Clin Res Ed). 1982; 285: 1005-8.
8. van Staa TP, Selby P, Leufkens HG, Lyles K, Sprafka JM, Cooper C. Incidence and natural history of Paget's disease of bone in Eng-

land and Wales. J Bone Miner Res. 2002; 17: 465-71.
9. Merlotti D, Gennari L, Galli B, Martini G, Calabrò A, De Paola V, et al. Characteristics and Familial aggregation of Paget's disease of bone in Italy. J Bone Miner Res. 2005; 20: 1356-64.
10. Cooper C, Schafheutle K, Dennison E, Kellingray S, Guyer P, Barker D. The epidemiology of Paget's disease in Britain: Is the prevalence decreasing? J Bone Miner Res. 1999; 14: 192-7.
11. Poór G, Donáth J, Fornet B, Cooper C. Epidemiology of Paget's disease in Europe: the prevalence is decreasing. J Bone Miner Res. 2006; 21: 1545-9.
12. Gennari L, Di Stefano M, Merlotti D, Giordano N, Martini G, Tamone C, et al. Prevalence of Paget's disease of bone in Italy. J Bone Miner Res. 2005; 20: 1845-50.
13. Rendina D, Gennari L, De Filippo G, Merlotti D, de Campora E, Fazioli F, et al. Evidence for increased clinical severity of familial and sporadic Paget's disease of bone in Campania, Southern Italy. J Bone Miner Res. 2006; 21: 1828-35.
14. Laurin N, Brown JP, Morissette J, Raymond V. Recurrent mutation of the gene encoding sequestosome 1 (SQSTM1/p62) in Paget's disease of bone. Am J Hum Genet. 2002; 70: 1582-8.
15. Hocking LJ, Lucas GJ, Daroszewska A, Mangion J, Olavesen M, Cundy T, et al. Domain specific mutations in sequestosome 1 (SQSTM1) cause familial and sporadic Paget's disease. Hum Mol Genet. 2002; 11: 2735-9.
16. Lucas GJ, Hocking LJ, Daroszewska A, Cundy T, Nicholson GC, Walsh JP, et al. Ubiquitin-associated domain mutations of SQSTM1 in Paget's disease of bone: evidence for a founder effect in patients of British descent. J Bone Miner Res. 2005; 20: 227-31.
17. Mays S. Archaeological skeletons support a northwest European origin for Paget's disease of bone. J Bone Miner Res. 2010; 25: 1839-41.
18. Bolland MJ, Tong PC, Naot D, Callon KE, Wattie DJ, Gamble GD, et al. Delayed development of Paget's disease in offspring inheriting SQSTM1 mutations. J Bone Miner Res. 2007; 22: 411-5.
19. Rea SL, Walsh JP, Ward L, Yip K, Ward BK, Kent GN, et al. A novel mutation (K378X) in the sequestosome 1 gene associated with increased NF-kappaB signaling and Paget's disease of bone with a severe phenotype. J Bone Miner Res. 2006; 21: 1136-45.
20. Morissette J, Laurin N, Brown JP. Sequestosome 1: mutation frequencies, haplotypes, and phenotypes in familial Paget's disease of bone. J Bone Miner Res. 2006; 21: P38-44.
21. Eekhoff EW, Karperien M, Houtsma D, Zwinderman AH, Dragoiescu C, Kneppers AL, et al. Familial Paget's disease in The Netherlands: occurrence, identification of new mutations in the sequestosome 1 gene, and their clinical associations. Arthritis Rheum. 2004; 50: 1650-4.
22. Ralston SH, Layfield R. Pathogenesis of Paget's disease of bone. Calcif Tissue Int. 2012; 91: 97-113.
23. Kurihara N, Hiruma Y, Yamana K, Michou L, Rousseau C, Morissette J, et al. Contributions of the measles virus nucleocapsid gene and the SQSTM1/p62(P392L) mutation to Paget's disease. Cell Metab. 2011; 13: 23-34.
24. Kurihara N, Zhou H, Reddy SV, Garcia Palacios V, Subler MA, Dempster DW, et al. Expression of measles virus nucleocapsid protein in osteoclasts induces Paget's disease-like bone lesions in mice. J Bone Miner Res. 2006; 21: 446-55.
25. Reddy SV, Singer FR, Roodman GD. Bone marrow mononuclear cells from patients with Paget's disease contain measles virus nucleocapsid messenger ribonucleic acid that has mutations in a specific region of the sequence. J Clin Endocrinol Metab. 1995; 80: 2108-11.
26. Gennari L, Merlotti D, Martini G, Nuti R. Paget's disease of bone in Italy. J Bone Miner Res. 2006; 21: P14-21.
27. Seton M, Choi HK, Hansen MF, Sebaldt RJ, Cooper C. Analysis of environmental factors in familial versus sporadic Paget's disease of bone - the New England Registry for Paget's Disease of Bone. J Bone Miner Res. 2003; 18: 1519-24.
28. Siris ES. Extensive personal experience: Paget's disease of bone. J Clin Endocrinol Metab. 1995; 80: 335-8.
29. Lucas GJ, Daroszewska A, Ralston SH. Contribution of genetic factors to the pathogenesis of Paget's disease of bone and related disorders. J Bone Miner Res. 2006; 21: P31-37.
30. Seton M. Diagnosis, complications and treatment of Paget's disease of bone. Aging Health. 2009; 5: 497-508.
31. Siris E, Roodman GD. Paget's disease of bone. 7th ed. Washington, DC: American Society for Bone and Mineral Research; 2008.
32. Seton M. Paget's disease of bone. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, eds. Rheumatology. 5th ed. Philadelphia, PA: Mosby Elsevier; 2010; 2021-2028.
33. Douglas DL, Duckworth T, Kanis JA, Jefferson AA, Martin TJ, Russell RG. Spinal cord dysfunction in Paget's disease of bone. Has medical treatment a vascular basis? J Bone Joint Surg Br. 1981; 63B: 495-503.

34. Siris ES. Epidemiological aspects of Paget's disease: family history and relationship to other medical conditions. Semin Arthritis Rheum. 1994; 23: 222-5.
35. Kanis JA, Evanson JM, Russell RG. Paget's disease of bone: diagnosis and management. Metab Bone Dis Relat Res. 1981; 3: 219-30.
36. Mangham DC, Davie MW, Grimer RJ. Sarcoma arising in Paget's disease of bone: declining incidence and increasing age at presentation. Bone. 2009; 44: 431-6.
37. Hansen MF, Seton M, Merchant A. Osteosarcoma in Paget's disease of bone. J Bone Miner Res. 2006; 21: P58-63.
38. Price CH. The incidence of osteogenic sarcoma in South-West England and its relationship to Paget's disease of bone. J Bone Joint Surg Br. 1962; 44-B: 366-76.
39. Ishikawa Y, Tsukuma H, Miller RW. Low rates of Paget's disease of bone and osteosarcoma in elderly Japanese. Lancet. 1996; 347: 1559.
40. Sun SG, Lau YS, Itonaga I, Sabokbar A, Athanasou NA. Bone stromal cells in pagetic bone and Paget's sarcoma express RANKL and support human osteoclast formation. J Pathol. 2006; 209: 114-20.
41. Fenton P, Resnick D. Metastases to bone affected by Paget's disease. A report of three cases. Int Orthop. 1991; 15: 397-9.
42. Tu SM, Som A, Tu B, Logothetis CJ, Lee MH, Yeung SC. Effect of Paget's disease of bone (osteitis deformans) on the progression of prostate cancer bone metastasis. Br J Cancer. 2012; 107: 646-51.
43. Cortis K, Micallef K, Mizzi A. Imaging Paget's disease of bone - from head to toe. Clin Radiol. 2011; 66: 662-72.
44. Redden JF, Dixon J, Vennart W, Hosking DJ. Management of fissure fractures in Paget's disease. Int Orthop. 1981; 5: 103-6.
45. [No authors listed]. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 25-1993. A 67-year-old man with osteolytic lesions of T11 and T12. N Engl J Med. 1993; 328: 1836-41.
46. Eekhoff ME, van der Klift M, Kroon HM, et al. Paget's disease of bone in The Netherlands: a population-based radiological and biochemical survey - the Rotterdam Study. J Bone Miner Res. 2004; 19: 566-70.
47. Reid IR, Davidson JS, Wattie D, Wu F, Lucas J, Gamble GD, et al. Comparative responses of bone turnover markers to bisphosphonate therapy in Paget's disease of bone. Bone. 2004; 35: 224-30.
48. Alvarez L, Guañabens N, Peris P, Vidal S, Ros I, Monegal A, et al. Usefulness of biochemical markers of bone turnover in assessing response to the treatment of Paget's disease. Bone. 2001; 29: 447-52.
49. Cundy T, Reid IR. Paget's disease of bone. Clin Biochem. 2012; 45: 43-8.
50. Russell RG, Smith R, Preston C, Walton RJ, Woods CG. Diphosphonates in Paget's disease. Lancet. 1974; i: 894-8.
51. Altman RD. Long-term follow-up of therapy with intermittent etidronate disodium in Paget's disease of bone. Am J Med. 1985; 79: 583-90.
52. Khairi MR, Altman RD, De Rosa GP, Zimmermann J, Schenk RK, Johnston CC. Sodium etidronate in the treatment of Paget's disease of bone. A study of longterm results. Ann Intern Med. 1977; 87: 656-63.
53. Boyce BF, Smith L, Fogelman I, Johnston E, Ralston S, Boyle IT. Focal osteomalacia due to low-dose diphosphonate therapy in Paget's disease. Lancet. 1984; i: 821-4.
54. Gibbs CJ, Aaron JE, Peacock M. Osteomalacia in Paget's disease treated with short term, high dose sodium etidronate. Br Med J. 1986; 292: 1227-9.
55. Altman RD. Long-term follow-up of therapy with intermittent etidronate disodium in Paget's disease of bone. Am J Med. 1985; 79: 583-90.
56. Dewis P, Prasad BK, Anderson DC, Willets S. Clinical experience with the use of two diphosphonates in the treatment of Paget's disease. Ann Rheum Dis. 1985; 44: 34-8.
57. Frijlink WB, Bijvoet OL, te Velde J, Heynen G. Treatment of Paget's disease with (3-amino-1-hydroxypropylidene)-1, 1-bisphosphonate (A.P.D.). Lancet. 1979; 1: 799-803.
58. Mautalen CA, Gonzalez D, Ghiringhelli G. Efficacy of the bisphosphonate APD in the control of Paget's bone disease. Bone. 1985; 6: 429-32.
59. Thiebaud D, Jaeger P, Burckhardt P. Paget's disease of bone treated in five days with AH-PrBP (APD) per os. J Bone Miner Res. 1987; 2: 45-52.
60. Adami S, Salvagno G, Guarrera G, Montesanti F, Garavelli S, Rosini S, et al. Treatment of Paget's disease of bone with intravenous 4-amino-1-hydroxybutylidene-1,1-bisphosphonate. Calcif Tissue Int. 1986; 39: 226-9.
61. Cantrill JA, Buckler HM, Anderson DC. Low dose intravenous 3-amino-1-hydroxypropylidene-1,1-bisphosphonate (APD) for the treatment of Paget's disease of bone. Ann Rheum Dis. 1986; 45: 1012-8.
62. Cundy T, McAnulty K, Wattie D, Gamble G, Rutland M, Ibbertson HK. Evidence for secular change in Paget's disease. Bone. 1997; 20: 69-71.
63. Yap AS, Mortimer RH, Jacobi JM, Galligan JP, Perry-Keene DA, Khafagi FA. Single-dose intravenous pamidronate is effective alternative therapy for Paget's disease refractory to calcitonin. Horm Res. 1991; 36: 70-4.

64. Ryan PJ, Gibson T, Fogelman I. Bone scintigraphy following intravenous pamidronate for Paget's disease of bone. J Nucl Med. 1992; 33: 1589-93.
65. Stone MD, Hawthorne AB, Kerr D, Webster G, Hosking DJ. Treatment of Paget's disease with intermittent low-dose infusions of disodium pamidronate (APD). J Bone Miner Res. 1990; 5: 1231-5.
66. Thiebaud D, Jaeger P, Gobelet C, Jacquet AF, Burckhardt P. A single infusion of the bisphosphonate AHPrBP (APD) as treatment of Paget's disease of bone. Am J Med. 1988; 85: 207-12.
67. Vega E, Gonzalez D, Ghiringhelli G, Mautalen C. Intravenous aminopropylidene bisphosphonate (APD) in the treatment of Paget's bone disease. J Bone Miner Res. 1987; 2: 267-71.
68. Watts RA, Skingle SJ, Bhambhani MM, Pountain G, Crisp AJ. Treatment of Paget's disease of bone with single dose intravenous pamidronate. Ann Rheum Dis. 1993; 52: 616-8.
69. Dodd GW, Ibbertson HK, Fraser TR, Holdaway IM, Wattie D. Radiological assessment of Paget's disease of bone after treatment with the bisphosphonates EHDP and APD. Br J Radiol. 1987; 60: 849-60.
70. Fenton AJ, Gutteridge DH, Kent GN, Price RI, Retallack RW, Bhagat CI, et al. Intravenous aminobisphosphonate in Paget's disease: Clinical, biochemical, histomorphometric and radiological responses. Clin Endocrinol. 1991; 34: 197-204.
71. Anderson DC, O'Driscoll JB, Buckler HM, Cantrill J, Brown JD. Relapse of osteoporosis circumscripta as a lytic ring after treatment of Paget's disease with intravenous 3-amino-1-hydroxypropylidene-1,1-bisphosphonate. Br J Radiol. 1988; 61: 996-1001.
72. Vellenga CJ, Pauwels EK, Bijvoet OL, Harinck HI, Frijlink WB. Quantitative bone scintigraphy in Paget's disease treated with APD. Br J Radiol. 1985; 58: 1165-72.
73. Gray RE, Yates AJ, Preston CJ, Smith R, Russell RG, Kanis JA. Duration of effect of oral diphosphonate therapy in Paget's disease of bone. Q J Med. 1987; 64: 755-67.
74. Percival RC, Watson ME, Williams JL, Kanis JA. Carcinoma of the prostate: remission of paraparesis with inhibitors of bone resorption. Postgrad Med J. 1985; 61: 551-3.
75. Wallace E, Wong J, Reid IR. Pamidronate treatment of the neurologic sequelae of pagetic spinal stenosis. Arch Intern Med. 1995; 55: 1813-5.
76. Pazianas M, Cooper C, Ebetino FH, Russell RGR. Long-term treatment with bisphosphonates and their safety in postmenopausal osteoporosis. Ther Clin Risk Manage. 2010; 6: 325-43.
77. Adamson BB, Gallacher SJ, Byars J, Ralston SH, Boyle IT, Boyce BF. Mineralisation defects with pamidronate therapy for Paget's disease. Lancet. 1993; 342: 1459-60.
78. Anderson DC, Richardson PC. Pamidronate and Paget's disease [letter]. Lancet. 1994; 343: 427.
79. Audran M, Clochon P, Etghen D, Mazieres B, Renier JC. Treatment of Paget's disease of bone with (4-chloro-phenyl) thiomethylene bisphosphonate. Clin Rheumatol. 1989; 8: 71-9.
80. Reginster JY, Jeugmans-Huynen AM, Albert A, Denis D, Deroisy R, Lecart, MP, et al. Biological and clinical assessment of a new bisphosphonate, (chloro-4 phenyl) thiomethylene bisphosphonate, in the treatment of Paget's disease of bone. Bone. 1988; 9: 349-54.
81. Brown JP, Hosking DJ, Ste-Marie L, Johnston CC Jr, Reginster J, Ryan WG, et al. Risedronate, a highly effective, short-term oral treatment for Paget's disease: A dose-response study. Calcif Tissue Int. 1999; 64: 93-9.
82. Miller PD, Brown JP, Siris ES, Hoseyni MS, Axelrod DW, Bekker PJ. A randomized, double-blind comparison of risedronate and etidronate in the treatment of Paget's disease of bone. Paget's Risedronate/Etidronate Study Group. Am J Med. 1999; 106: 513-20.
83. Douglas DL, Duckworth T, Kanis JA, Preston C, Beard DJ, Smith TW, et al. Biochemical and clinical responses to dichloromethylene diphosphonate (Cl2PAGET'S) in Paget's disease of bone. Arthritis Rheum. 1980; 23: 1185-92.
84. Adami S, Guarrera G, Salvagno G, Spiazzi G, Marini G, Rosini S, et al. Sequential treatment of Paget's disease with human calcitonin and dichloromethylene diphosphonate (Cl2PAGET'S). Metab Bone Dis Relat Res. 1984; 5: 265-7.
85. Yates AJ, Percival RC, Gray RE, Atkins RM, Urwin GH, Hamdy NA, et al. Intravenous clodronate in the treatment and retreatment of Paget's disease of bone. Lancet. 1985; i: 1474-7.
86. Filipponi P, Pedetti M, Beghe F, Giovagnini B, Miam M, Cristallini S. Effects of two different bisphosphonates on Paget's disease of bone: ICTP assessed. Bone. 1994; 15: 261-7.
87. Adami S, Mian M, Gatti P, Rossini M, Zamberlan N, Bertoldo F, et al. Effects of two oral doses of alendronate in the treatment of Paget's disease of bone. Bone. 1994; 15: 415-7.
88. Adami S, Zamberlan N, Mian M, Dorizzi R, Rossini M, Braga B, et al. Duration of the effects of intravenous alendronate in postmenopausal women and in patients with primary hyperparathyroidism and Paget's disease of bone. Bone Miner. 1994; 25: 75-82.

89. Khan SA, Vasikaran S, McCloskey EV, Beneton MN, Rogers S, Coulton L, et al. Alendronate in the treatment of Paget's disease of bone. Bone. 1997; 20: 263-71.
90. O'Doherty DP, Bickerstaff DR, McCloskey EV, Eyres KS, Kanis JA. Radiographic healing of osteolytic Paget's disease of the tibia with alendronate. J Orthop Rheumatol. 1991; 4: 153-7.
91. Grauer A, Heichel S, Knaus J, Dosch E, Ziegler R. Ibandronate treatment in Paget's disease of bone. Bone. 1999; 24: 87-9.
92. Papapoulos SE, Hoekman K, Lowik CW, Vermeij P, Bijvoet OL. Application of an in vitro model and a clinical protocol in the assessment of the potency of a new bisphosphonate. J Bone Miner Res. 1989; 4: 775-81.
93. Schweitzer DH, Zwinderman AH, Vermeij P, Bijvoet OL, Papapoulos SE. Improved treatment of Paget's disease with dimethylaminohydroxypropylidene bisphosphonate. J Bone Miner Res. 1993; 8: 175-82.
94. Filipponi P, Cristallini S, Policani G, Casciari C, Gregorio F. Paget's disease of bone: benefits of neridonate as a first treatment and in cases of relapse after clodronate. Bone. 1998; 23: 543-8.
95. Adami S, Bevilacqua M, Broggini M, Filipponi P, Ortolani S, Palummeri E, et al. Short-term intravenous therapy with Neridronate in Paget's disease. Clin Exp Rheumatol. 2002; 20: 55-8.
96. Reid IR, Miller P, Lyles K, Fraser W, Brown JP, Saidi Y, et al. Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. N Engl J Med. 2005; 353: 898-908.
97. Reid IR, Lyles K, Su G, Brown JP, Walsh JP, del Pino-Montes J, et al. A single infusion of zoledronic acid produces sustained remissions in Paget's disease: data to 6.5 years. J Bone Miner Res. 2011; 26: 2261-70.
98. Langston AL, Campbell MK, Fraser WD, MacLennan GS, Selby PL, Ralston SH, et al. Randomized trial of intensive bisphosphonate treatment versus symptomatic management in Paget's disease of bone. J Bone Miner Res. 2010; 25: 20-31.
99. Singer FR, Krane SM. Paget's disease of bone. In: Avioli LV, Krane SM, eds. Metabolic bone disease and clinically related disorders. 2nd ed. Philadelphia, PA: W.B. Saunders Company; 1990; 546-615.
100. Kanis JA, Horn DB, Scott RD, Strong JA. Treatment of Paget's disease of bone with synthetic salmon calcitonin. Br Med J. 1974; 3: 727-31.
101. Schwarz P, Rasmussen AQ, Kvist TM, Andersen UB, Jørgensen NR. Paget's disease of the bone after treatment with denosumab: a case report. Bone. 2012; 50: 1023-5.
102. Goutallier D, Sterkers Y, Cadeua F. Experience de la prosthese totale au cours de la coxopathie pagetique. Rhumatologie. 1984; 36: 81-2.
103. Bowie HIC, Kanis JA. Calcitonin in the assessment and preparation of patients with Paget's disease for surgery. In: Kanis JA, ed. Bone disease and calcitonin. Eastbourne, UK: Armour Pharmaceuticals; 1976; 61-9.
104. Bidner S, Finnegan M. Femoral fractures in Paget's disease. J Orthop Trauma. 1989; 3: 317-22.
105. Bradley CM, Nade S. Outcome after fractures of the femur in Paget's disease. Austral NZ J Surg. 1992; 62: 39-44.
106. Louette L, Lammens J, Fabry G. The Ilizarov external fixator for treatment of deformities in Paget's disease. Clin Orthop Rel Res. 1996; 323: 298-303.
107. Sochart DH, Porter ML. Charnley low-friction arthroplasty for Paget's disease of the hip. J Arthroplasty. 2000; 5: 210-9.
108. Richardson PC, Cantrill JA, Anderson DC. Experience of treating 218 patients with Paget's disease of bone using intravenous 3-aminohydroxypropylidene 1-1 bisphosphonate (Pamidronate, APD). In: Cohn DV, Glorieux FH, Martin TJ, eds. Calcium regulation and bone metabolism. New York: Elsevier; 1990; 509-14.
109. Gutteridge DH, Ward LC, Stewart GC, Retallak RW, Will RK, Prince RL, et al. Paget's disease: acquired resistance to one aminobisphosphonate with retained response to another. J Bone Miner. 1999; 2: 79-84.