**García Arias M[1], Torrijos Eslava A[2]**
1 Médico Residente de 4º año - Servicio Reumatología - H. U. La Paz - Madrid
2 Reumatólogo - Responsable de la Unidad Metabólica Ósea - Servicio de Reumatología - H. U. La Paz - Madrid

# Treatment of Paget's disease of bone

Correspondence: Antonio Torrijos Eslava - Servicio de Reumatología - Hospital Universitario La Paz - Paseo de la Castellana, 261 - 28046 Madrid (Spain)
e-mail: atenino@aten.jazztel.es

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## Introduction

Paget's disease of bone (PDB) is a chronic and focussed skeletal disorder, whose cause is unknown. The disease is located in the osteoclasts, which increase in number, size and activity. Bone turnover accelerates, with an increase in bone resorption, followed by excessive and disorganised formation. The result is bone which is not laminar (plexiform bone) highly vascularised, increased in volume, less compact and more susceptible to fracture or deformation. It is usually diagnosed at over 60 years of age, being infrequent below 40 years of age. It slightly predominates in males. It is the most common metabolic bone disease after osteoporosis[1].

It is considered to be a multifactorial disease with the involvement of environmental and genetic factors.

Its main clinical manifestations are bone deformity and pain. During its evolution various complications may appear, the most frequent being degenerative arthropathy in its vicinity, neurological changes due to compression, fractures, cardiac pathology, disorders of the metabolism and of bone remodelling.

The diagnosis is based on clinical manifestations, raised levels of biochemical markers for bone remodelling (essentially, alkaline phosphatase – AP) and radiology.

There is no curative treatment, but the antiresorptives, especially the diphosphonates, are efficacious in controlling the activity and progression of the disease. The therapeutic objectives are to eliminate bone pain, normalise bone remodelling, re-establish normal bone structure and prevent recurrence and complications.

## Indications

The treatment of PDB can be divided into symptomatic treatment and specific treatment.

Symptomatic treatment is intended, primarily, to eliminate pain. Simple analgesics, non-steroidal anti-inflammatories, opioids and low doses of tricyclical antidepressives control the pain. In addition, rehabilitation, and mobility aids, such as walking sticks, improve the quality of life of the patient.

In the case of fracture, deformity or pagetic arthropathy surgery may be indicated.

The indications for establishing a specific treatment for the disease are not universally accepted due to the absence of evidence from the controlled clinical trials that medical treatment not only suppresses markers for bone remodelling, but also reduces reported complications.

There are relative and absolute indications, and it is always necessary to take into account the age of the patient, their life expectancy and their clinical state. The specific treatment is aimed at suppressing osteoclast activity in the pagetic lesions.

Salmon calictonin has been used for over 30 years. However, clinical and biochemical remission in PDB is exceptional, since at 6 months a plateau is reached and on suspending the drug a progressive increase in biochemical markers is observed, and nowadays it has been replaced by other drugs.

Since the introduction of the diphosphonates these have assumed a principal role in the treatment of this disease. The drugs used nowadays are aminated diphosphonates, which have a much more intense and much more prolonged antiresorptive action. They slow osteoclast activity to normal levels, are easy to administer and have an acceptable level of tolerance. They do not alter mineralisation, and normalise bone structure at a histological level.

The indications for the treatment of PDB have been listed in various publications[2-11]. They differ from one author to another, but a number of absolute indications have been established, which are not disputed, for the initiation of treatment. On the other hand, there is a series of **relative indications** which are the cause of major discussions, since they are based on criteria which are not supported by sufficient scientific evidence. The clearest and most discussed example is the active asymptomatic disease shown only by biochemical markers or by imaging techniques, in which the treatment is intended to achieve control of the osteoclast activity, and of the disease, as well as avoiding its complications. However, there is no scientific evidence which indicates that their appearance is avoided.

However, treatment in those asymptomatic patients with normal biochemical markers and normal bone gammagraphy, would not be indicated, although radiology shows lesions compatible with PDB[2].

The **absolute indications** established for the treatment of PDB are:

1. In those cases in which the symptoms are caused by the disease, such as: primary bone pain caused by the disease, or due to a pathological fracture, pagetic radiculopathy, arthropathy due to lesions in the neighbouring joints, deafness, neurological compression (especially the medullar) or other neurological symptoms associated with PDB.

2. In the case of programmed orthopaedic surgery on a pagetic bone, in order to minimise bleeding in the active disease.

3. To avoid the hypercalcemia which may occur during prolonged immobilisation.

4. Another indication, for many authors, would be to diminish its local progression and reduce the risk of future complications in those patients with the active asymptomatic disease, and in whom the location of the disease, and its degree of metabolic hyperactivity, may carry a risk of progression and complications.

There is indirect evidence that aggressive treatment of PDB is associated with the prevention of progression, and a reduction in the risk, of future complications. This evidence is:

1. Failures in the treatment of the disease are associated with future destruction of bone and the progression of deformities.

2. Efficacious treatments are associated with the normal restoration of new bone deposits. In addition, a study has shown that facial and cranial deformities improve after treatment.

Hence, in the light of these findings, various authors conclude that good clinical practice would include treatment both symptomatic patients, whose alterations may respond to a reduction in abnormal remodelled bone, as well as asymptomatic patients in whom the disease is active which may happen with future complications.

In 2008, Devogelaer et al.[5], produced a consensus document in which the indications for the treatment of asymptomatic PDB are presented. These indications are:

1. Age of diagnosis before 50 years of age.

2. Location of the bone lesions: in limbs, near the joints, due to the risk of secondary arthrosis; lytic lesions, due to the risk of fracture; in the hip; in the cervical and thoracic spine, due to the risk of neurological complications, spinal stenosis or pagetic steal syndrome; in the cranium, especially locations at its base, due to the risk of loss of hearing and/or other neurological complications.

3. Raised levels of total AP, greater than twice the upper limit for normality.

4. Programmed orthopaedic intervention on pagetic bone.

In 2002 Selby et al.[3], established grades of recommendation for the treatment of symptoms of PDB, according to the level of the evidence which supports it. Thus:

1. Bone pain is a clear indication for treatment (Grade A)

2. Fracture is a complication of the disease. Treatment solely to reduce the risk of fracture, or after a fracture, to improve its repair, is not indicated (Grade C).

3. The effect of antipagetic therapy on bone deformity is not clear (Grade C). However, the use of diphosphonates may be justified in facial deformities due to the disease (Grade B).

4. Different studies have suggested that the diphosphonates improve the osteolytic lesions in PDB. However, the clinical significance is not clear, and no specific recommendations are made for the treatment in osteolytic disease in the absence of other indications for treatment (Grade C).

5. In the prevention of arthrosis, whose presence is increased in PDB, there is no evidence that the treatment prevents its development or progression (Grade C).

6. A very common complication of the disease is deafness, but the effect of antipagetic treatment in the development and progression of deafness is not totally clear. In patients with pagetic affectation at the base of the cranium, treatment would be considered to minimise the risk of loss of hearing (Grade B).

7. The effect of the diphosphonates on the quality of life of patients with PDB has only been evaluated in two studies which did not show statistically significant differences (Grade C).

8. Medullar compression is a relatively rare complication of PDB. Various studies have been published which show that calcitonin and diphosphonates improve neurological function in these patients.

9. It has been suggested that antipagetic treatment may help to reduce bleeding in patients undergoing surgery in pagetic bone. However, this has never been demonstrated in controlled clinical trials (Grade C).

10. A rare complication of PDB is hypercalcemia due to the combination of an increase in remodelled bone and immobility.

11. In terms of sarcoma, there is no scientific evidence that treatment of the disease diminishes its development or progression in PDB (Grade C).

12. Finally, with reference to treatment of PDB in young patients, some experts warn that they should always receive treatment, independently of any other indications. However, there is no scientific evidence to support this opinion (Grade C).

## Drugs used in the treatment of PDB

### General characteristics

The drugs most used, and of first choice, are the diphosphonates. Their use in PDB began in 1970, and with the appearance of the aminated diphosphonates the therapeutic response has been stronger. They are synthetic analogues of the pyrophosphates and are characterised by their high antiresorptive power in the bone remodelling cycle. Their accumulation in the bone contributes to the maintenance of the reduction in markers for bone turnover for years.

**Physical-chemical properties:**

All the diphosphonates share a common chemical structure in which a carbon atom is bonded to two phosphate groups (P-C-P), whose negative charge explains its affinity to bone tissue. The power of its action comes from the lateral chains united with a common nucleus, and it has been demonstrated that the presence of nitrogenated compounds in these lateral chains give it its strong activity. Its absorption when taken orally is very low, no higher than 1%, which means that it should be administered after prolonged fasting. Its average blood life is approximately 1 hour, but its level of stable incorporation into the bone is 20% of the dose absorbed. However, its average life in bone is greater than 10 years. The diphosphonates are eliminated through urine, which means that care should be taken in patients with chronic renal insufficiency since that may alter the metabolism of the drug and worsen previous renal function[12].

**Action mechanism:**

The diphosphonates are selective inhibitors of osteoclast action in the bone remodelling cycle. The effect is achieved both by slowing the differentiation of common precursor cells (haematopoietic stem cells), and by favouring the apoptosis of the mature osteoclasts.

There are two principal action mechanisms. The older and less powerful diphosphonates are captured by the osteoclasts and converted into toxic analogues of ATP. However, the most powerful diphosphonates act by inhibiting farnesyldiphosphate synthase (FPP-synthase), an enzyme of the cholesterol synthesis pathway derived from mevalonate. These diphosphonates, which contain nitrogen, indirectly suppress the geranylgeranylation process of the proteins, which in turn inhibits osteoclast activity.

Lately, other actions of diphosphonates have been described which involve the osteoblast-osteocyte cell line. *In vitro*, the diphosphonates have been shown to have a protective action on the integrity of the bone matrix through an inhibition of the apoptosis of the osteocytes. Recent studies show that the diphosphonates may act to facilitate the recruitment of the osteoblasts, as well as stimulating in the aforementioned cell line the production of an antiresorptive compound: osteoprotegerin[13].

**Method of administration:**

Given that the diphosphonates have a low oral absorption, they should be administered after a prolonged period of fasting. They should be ingested with a sufficient quantity of water (100 ml or more) in order to favour their dispersion in the stomach. The taking of other liquids or foods should be avoided, for at least half an hour after their administration. In addition, patients should remain upright, preferably standing, during this period, in order to avoid gastro-oesophageal reflux, and its potential lesions. In some patients hypocalcemia and vitamin D deficit is observed, which may result in mineralisation disorders, for which reason calcium and vitamin D supplement should be given.

**Secondary effects:**

In general, these are well-tolerated drugs, if they are administered correctly. In respect of oral diphosphonates, the most frequent secondary effects are those which affect the higher digestive system: erosions, gastric ulcers, and, in more serious cases, oesophagitis and oesophageal stenosis. Less frequent are those adverse ocular effects such as conjunctivitis, scleritis, uveitis...

Notable among the adverse effects of intravenous diphosphonates are: phlebitis, which may appear in up to 18% of patients; transitory febricula and shivering (10-41%); pseudo-flu syndrome (20%) hypocalcemia (5-17%), which can be avoided by administering 1 gram of calcium a day orally, for 7-14 days following the administration of the treatment.

**Drugs approved in Spain:**

**Etidronate** was the first diphosphonate used in PDB. The dose used was 5 mg/kg weight/day for 6 months. It achieved a reduction in bone pain in approximately 50% of patients, and the reduction in bone turnover varied between 40% and 60%. At the end of treatment a reactivation was observed for a few months, and in some, a resistance to the drug in later treatments was observed[12,14-16].

**Tiludronate** is 3-10 times more powerful than etidronate. The optimum dose for the treatment of

PDB is 400 mg daily, taken orally, over 3 months. A reduction in AP has been seen, which varies between 30.5% and 76.1% depending on the study, and a normalisation of the values of AP varying between 27% and 38% at the end of treatment, remaining normalised after a year in 69% of cases[17-21].

The response to tiludronate usually appears during the first 3 months and may last 18 months. It is recommended that a new cycle of treatment is not repeated before 6 months have passed.

**Risedronate:** the recommended dose is 30 mg/day over 2 months. It reduces by 60-70% the levels of markers for bone turnover in most patients, and its effects continue for 2 years after the end of treatment[13,22-28].

Various studies published have shown that risedronate is efficacious in the reduction of pain, and even in its disappearance. In terms of radiology, there is evidence of a reduction in osteolytic activity in the first six months of treatment, which was correlated with the markers for the activity of the disease[29]. In the histological analyses, the formation of lamellar bone was observed, without evidence of a mineralisation disorder in the bone tissue not affected by Paget's.

The use of **pamidronate** is exclusively intravenous. The total dose approved is 180-210 mg, in two forms of administration: one is a dose of 30 mg once a week for 6 weeks; the other is an initial dose of 30 mg, followed by 60 mg every 2 weeks until the dose is complete. It achieved an alleviation of pain in 70% of patients, and remission, with suppression of bone resorption following the reduction in AP. This reduction is produced more rapidly than with other diphosphonates and the remission time is greater in cases of low activity. The remission according to the series was 50% after 2 years and 25% after 4 years. This suppression has been evaluated by bone gammagraphy with a reduction in capture. Histologically, there was a reduction in remodelled bone, with formation of laminated bone and with no alterations in bone mineralisation[30-35].

**Zoledronate**, recently incorporated into the treatment of PDB, is a third generation diphosphonate, and the one which currently has the greatest antiresorptive power. A second atom of N achieves a radical imidazole heterocycle. The dose is 5 mg i.v., administered in a single infusion. In the most important study carried out, zoledronate was compared with risedronate in 350 patients; they considered there to have been a clinical response when the level of AP was reduced by more than 75% from its initial level, or was normalised. A response of 96.6% was observed with zoledronate and of 74.3% with risedronate, with a normalisation of AP of 88.6% and 57.9% respectively. After six months of treatment, the loss of response was 0.9% for zoledronate and 25.6% for risedronate ($p< 0.001$). In the long term control zoledronate maintained bone turnover within margin of reference values during the 24 months after the start of treatment[36-38].

**Other diphosphonates being used in PDB, or in the experimental phase:**

Among these drugs we have one approved in other countries, and others in experimentation.

**Clodronate:** this is marketed for tumoral hypercalcemia. In the clinical trials the doses used have varied between 400 and 2,400 mg/day. The optimum dose was 800 mg/day over 6 months, taken orally. Its efficacy is similar to that of etidronate[39].

**Alendronate:** this is an aminodiphosphonate. Its usual regime is 40 mg/day, taken orally over 3-6 months. It produces a normalisation in biochemical markers in more than 50% of cases. It is not indicated for the treatment of PDB in our country, but it has been approved by the FDA.

**Neridronate:** there are few studies available on this drug. There is a study with 32 patients to whom were administered i.v. neridronate, which observed a normalisation of AP of 65%, with the response being maintained over 12 months[40].

**Ibandronate:** a clinical trial with 24 patients to whom were administered 2 mg i.v. of this drug observed a normalisation of AP of 45%, with the response maintained over 12 months[41].

**Olpadronate:** there are also few studies carried out on this drug. Administered at a dose of 200 mg, orally over 12 days, it showed a normalisation of AP of 87%, with the response maintained for 12 months in 60% of patients[42].

**Future therapies:** new treatments for PDB continue to be studied, among which is subcutaneous recombinant **osteoprotegerin**. Recently a study has been published in which two twins with juvenile PDB were used, which observed a suppression of bone resorption[43].

## Monitoring of treatment

In symptomatic cases, the improvement of clinical manifestations is the essential parameter to be taken into account as the indicator of therapeutic efficacy. Although improvements in radiological lesions and a reduction in gammagraphy capture have been suggested, all authors accept the convenience of following the therapeutic response through markers for bone turnover. Among these are:

1. Total blood AP, the most-used biochemical marker[1]. It has good reproducibility and sensitivity and, although the ideal is the normalisation of these parameters, in the last clinical trial a good clinical response was considered to have occurred when there was a reduction of at least 50-75% in values prior to treatment. Some authors recommend determining the level of AP every three months during the first 6 months and then at intervals of 6 months.

2. Biochemical markers for bone resorption, such as deoxypyridinoline, and other more modern markers (CTx, NTx), respond more rapidly to treatment. Their nadir is within the month of initiation of treatment. The correlation between these markers and total AP is good[3].

Bone gammagraphy is not a good method for monitoring the response to treatment, since there

is a considerable delay, of approximately six months, between the biochemical response and the bone gammagraphy. In addition, patients are exposed to radiation. However, in monostotic PDB, and in those patients in whom pain persists in spite of the normalisation of the biochemical markers, repeating the bone gammagraphy may be useful[3].

## Indications for renewing treatment of a patient with PDB

Giving a further cycle or dose of treatment in PDB is recommended when there is a relapse in the disease or when the symptoms persist. In the case of pain, it should be confirmed that it is of pagetic origin, completely discounting other causes of pain[3].

Although there is no supporting evidence in the clinical trials carried out, it is generally accepted that an increase in AP of 25% from the baseline or the upper limit of normality after normalisation indicates a significant biochemical relapse[2,3,5].

Other authors also recommend returning to treatment when lytic lesions reappear in the large bones[2,5].

The effect of the diphosphonates appears at 3 months from the initiation of treatment and their maximum effect is at 6 months, therefore it would appear logical not to initiate another treatment until this six months has elapsed.

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