Continuing medical education

Treatment of Paget’s Disease of Bone

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ABSTRACT
Paget’s disease of bone is the paradigm of bone focal distortion with accelerated bone turnover. Over the years, a number of different drugs have been used to control its activity but, since bisphosphonates were introduced for the treatment of the disease, they have become the preferred treatment. This review will update the therapeutic indications, available drugs and therapeutic response monitoring.

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Introduction

Paget’s disease of bone (PD), also known as osteitis deformans, was first described in 1876 by the English surgeon Paget.\(^1\) It is a focal skeletal disorder in which bone remodeling is accelerated, with an initial increase in bone resorption followed by excessive osteoblastic activity. As a result, there is deformity and enlargement of the bone with a defective and disorganized pattern (plexiform bone) and therefore more susceptible to fractures and deformities.

Its etiology is unknown. The current etiopathogenic hypothesis is complex, and includes an initial sensitization phenomenon by an environmental agent of the appropriate genetic determinant, leading to the development of the disease.\(^2\)

Its diagnosis is rare before age 40, and in most series predominates in males. Its geographical distribution is uneven with areas of high prevalence, with familial aggregation detected in most series.\(^3\)

Most patients are asymptomatic, with the predominant form being polyostotic involvement. The main symptoms, when present, are bone pain and deformity. The diagnosis is made with imaging by plain radiography, and scintigraphy with Technecium\(^{99}\), something that enables the making of a topographic map of the disease. Other imaging techniques are resorted to in cases that raise diagnostic doubts. The evaluation of biochemical markers of bone turnover provides indirect information of both disease activity and the therapeutic response.

On the basis of pathogenic features of PD, treatment with antiresorptive drugs is used to achieve normalization of bone turnover. Since the introduction of bisphosphonates in 1970,
these agents have become the treatment of choice because of their better efficacy and safety profile compared to then used calcitonin.

### Targets and Therapeutic Indications

Before discussing the main drugs available and their individual characteristics, let us define the goals of treatment and the main indications.

The goal of treatment is control of symptoms and normalization of remodeling markers, all without altering the mineralization and normalizing bone structure. What we are trying to achieve is to prevent future complications with early therapeutic intervention, a fact that at present has no evidence to support it.

### Treatment

There are widely accepted guidelines, including consensus recommendations as described below:

- **Symptomatic patients** (bone pain from the disease or secondary to fragility fractures, neurological compression syndromes, heart failure due to treatment).
- **Preoperative treatment** of elective surgery on the Pagetic bone to prevent intraoperative bleeding complications.
- **Hypercalcemia**. Appears infrequently and occurs in patients with extensive involvement and after periods of prolonged immobilization.
- **Impact of critical areas susceptible to developing severe complications** (long bones, skull base, spine especially above L2 and adjacent to large joints, lytic lesions).

The dilemma of therapeutic intervention in PD is present in asymptomatic patients with biochemical or imaging activity. Treatment aims to prevent development of complications with early intervention. Recommendations are based on studies of low statistical power and theoretical considerations. In fact in 2010, the PRISM study was published, comparing two treatment strategies with bisphosphonates; an aggressive approach in which patients were treated when there was alkaline phosphatase elevation whether symptomatic or not, and the outcome being the primary biochemical normalization; and another, treating only symptomatic patients. The intention was to determine whether an intensive strategy in asymptomatic patients but with biochemical activity prevented the development of further complications. No differences were found between groups in the prosthetic hip replacement numbers, number of fractures, hearing loss or improved quality of life. The study has limitations in design and a limited follow-up time (3 year on average), as well the fact that zoledronic acid, the most potent drug available at present, was not evaluated.

Therefore, well-designed studies are needed to determine long-term prevention of the development of complications in PD and to provide data that may condition decisive therapeutic decisions.

Anyway, even despite the lack of evidence, the tendency is to treat patients who have greater risk of future complications.

### Pharmacotherapy

#### Modulators of the Activity

The mainstay of treatment of the PD is the use of antiresorptive agents in order to reduce high bone turnover and osteoclast activity. Over the years various drugs have been used, but since the introduction of bisphosphonates in 1970, they have become the antiresorptive treatment of choice.

All bisphosphonates share a common chemical structure (two phosphate molecules attached to a carbon atom). They are synthetic analogs of pyrophosphate with antiresorptive potency, and act by reducing bone remodeling and resorption. The effect is achieved by both osteoclast differentiation of stem cells as common precursor, promoting apoptosis of mature osteoclasts. According to their structure, they are classified depending on whether they contain an amino group or not (Table 1), with amino-bisphosphonates having demonstrated a better efficacy and safety profile.

Bisphosphonates approved for use in the PD marketed in Spain are: pamidronate, risedronate and zoledronic acid (amino) and non-amino group drugs such as etidronate and tiludronate (Table 2). Other bisphosphonates have demonstrated efficacy in Paget’s disease but have not been marketed for this indication in Spain (alendronate, ibandronate, neridronate, olpadronate and clodronate).

#### First generation bisphosphonates

Non-amino bisphosphonates have been displaced by the amino-bisphosphonates as the treatment of choice, and the former are used only in case of contraindication to the latter compounds.

**Etidronate** was the first bisphosphonate used in PD and showed a greater reduction in bone turnover than calcitonin, the antiresorptive agent used at that time. However, the detection of alterations in bone mineralization secondary to the use of etidronate limited the dose and duration of use (not to exceed 6 months). Early reactivation of the disease and the emergence of resistance in some patients were also noted.

**Tiludronate** proved superior to etidronate without the appearance of alterations in mineralization, achieving a reduction of alkaline phosphatase between 30.5% and 76.1% which remained at 12 months in up to 69% of patients. **Clodronate** has no indication for PD in Spain. The efficacy is similar to that of etidronate, although with longer periods of remission. It does not have effects on bone mineralization.

#### Table 1

<table>
<thead>
<tr>
<th>Non-Aminated Bisphosphonates</th>
<th>Aminated Bisphosphonates</th>
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<tbody>
<tr>
<td>Etidronate</td>
<td>Pamidronate</td>
</tr>
<tr>
<td>Tiludronate</td>
<td>Alendronate</td>
</tr>
<tr>
<td>Clodronate</td>
<td>Risedronate</td>
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<td></td>
<td>Ibandronate</td>
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<td></td>
<td>Neridronate</td>
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<td>Olpadronate</td>
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<td></td>
<td>Zoledronic acid</td>
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</tbody>
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#### Table 2

Bisphosphonate Doses Approved in Spain for PD.

<table>
<thead>
<tr>
<th>Bisphosphonate</th>
<th>Dose</th>
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<tbody>
<tr>
<td>Etidronate</td>
<td>5 mg/kg/day, 6 months, oral</td>
</tr>
<tr>
<td>Tiludronate</td>
<td>400 mg/day, 3 months, oral</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>30 mg/day 2 months, oral</td>
</tr>
<tr>
<td>Clodronate</td>
<td>30 mg/week (6 doses) or a first dose of 30 mg then 60 mg/2 week (3 doses) (total dose 180–210 mg)</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>5 mg IV single dose</td>
</tr>
</tbody>
</table>
• Amino-bisphosphonates
The treatment of Paget's disease suffered a shift in 1979 with the publication of a study using oral pamidronate. An antiresorptive, it led to rapid restoration of normal bone formation. This study led to a series of publications on the use of pamidronate in PD, both orally and intravenously, demonstrating its superiority over other non-aminated bisphosphonates. The currently approved regimen is intravenous (doses in Table 2).

Table 2

No alterations in bone mineralization have been described, but resistance has been detected on those patients retreated with this drug. Later came the development of another amino-bisphosphonate, alendronate. Its efficacy was established in two randomized clinical trials, one alone and another vs placebo, or etidronate, showing a normalization of the alkaline phosphatase in 60%–70% of patients at 6 months. In 2004, a comparative study of oral alendronate vs IV pamidronate was published. No differences were found between both treatment groups when it came to patients not receiving bisphosphonates, but alendronate was superior in patients previously treated with pamidronate. Alendronate has no indication for PD in our country.

In parallel with alendronate, risedronate was developed, demonstrating its efficacy in open studies and against etidronate, reducing alkaline phosphatase in 66%–80%. Currently the amino-bisphosphonate risedronate is the only oral drug indicated in our country for PD.

The most recently introduced bisphosphonate in the treatment of PD is zoledronic acid. It is a bisphosphonate that has shown affinity for hydroxyapatite in vitro and the most potent antiresorptive we currently have. It is administered as a single intravenous infusion of 5 mg. Two randomized trials comparing single infusion zoledronic acid with risedronate oral exist. Zoledronic acid improved response at 6 months in 96% of responding patients compared to 74.3% in the risedronate group, and was associated with a faster and maintained response. These results will be confirmed in a 2 and 5-year extension study.

In 2007, the results of a study comparing different IV bisphosphonates were published. Compared to pamidronate, another bisphosphonate indicated intravenously in our country for PD, zoledronic acid was more effective and associates with an earlier response, with more pamidronate infusions required and with the development of resistance to treatment. Further studies are needed to expand the evidence, but for now zoledronic acid is better, with results in both induction and maintenance of remission.

• Other drugs
Although the new bisphosphonates are drugs with a good safety profile and relatively well tolerated, there are situations in which we cannot use them. In these cases the peptide hormone calcitonin, capable of inhibiting bone resorption, could be useful. It was used in the treatment of PD, but relapses after discontinuation of treatment and a plateau effect after approximately 4–6 months of treatment, relegated it to the backburner after the appearance of bisphosphonates.

Other therapies such as gallium nitrate are used only in patients with serious complications or bisphosphonate resistance because it has a limited effect and frequent recurrences. Mithramycin is no longer used due to its renal, bone marrow and liver toxicity.

• Calcium and vitamin D
Another fundamental aspect in the treatment of PD is calcium (1000 mg) and vitamin D (400–800 IU) supplementation in patients receiving antiresorptive therapy to prevent hypocalcemia and secondary hyperparathyroidism.

The standard dose is indicated, but must be individualized by laboratory testing, enhancing supplementation in the case of zoledronic acid in the days before and after its infusion.

Symptoms
Apart from specific treatment, we must effectively manage symptoms. The main symptom is pain, which may not always be derived from the activity of the disease, but may be secondary to complications and localized lesions. It is mainly treated with NSAIDs and analgesics, with tricyclic antidepressants being useful in some cases.

On the other hand, we should not forget orthotic treatment, walking and hearing aids, canes, etc., which may help improve the quality of life of patients.

Surgery
There are five main indications for surgical treatment:

1. Fractures.
2. Deformity: that cause pain when they are difficult to control or associated with bone fissures, corrected through the use of osteotomy.
3. Pagetic arthropathy: arthroplasty when symptoms are not effectively controlled with medical treatment.
4. Entrapment neuropathies and myelopathies.
5. Cancer.

Monitoring of Therapeutic Response
Biomarkers of bone turnover indirectly estimate the activity of the disease and are therefore used in the assessment of treatment response in conjunction with the clinical response. Currently, despite the development of new markers, total alkaline phosphatase (TAP) remains the marker of choice for monitoring response to treatment. Historically, therapeutic response has been defined as a decrease of at least 25% of TAP; however, with current drugs, most studies measuring response set their objective as the normalization of biochemical markers or alternatively, as the decrease of at least 75% of initial TAP.

However, and given the spectrum of presentations of PD, there are cases where other markers are more useful than TAP. In patients with monostotic involvement with normal TAP or patients with liver disease, the use of more sensitive markers such as alkaline phosphatase (AP) and the aminoterminal propeptide of procollagen type I (APPPI) is recommended.

Regarding the role of bone scintigraphy in monitoring therapeutic response, it has been relegated to isolated cases in which the patient is exposed to radiation and there is a delay of approximately 6 months with respect to the biochemical response. In patients with monostotic PD and normal bone turnover markers at baseline, it could be useful from 6 to 12 months after treatment.

As for biomarker monitoring intervals should be individualized based on treatment and individual patient characteristics. A possibility would be the quarterly analytical monitoring the first 6 months and then every 6 months.
Retreatment

The need for a new cycle of treatment occurs when there is a new increase of bone remodeling. At the onset of the disease or after the increase of the biomarkers discussed in the previous section, it is important to determine parameters that measure activity. Therefore, and according to the available evidence, we recommend a new course of treatment in cases of:

- Recurrence of symptoms and/or
- Increased alkaline phosphatase above normal, or more than 25% of the nadir reached.

To clarify, since the effect of bisphosphonate treatment usually appears 3–6 months after onset of treatment, it is prudent to wait 6 months before determining the need for a new therapeutic intervention.

Disclosures

The authors have no disclosures to make.

