ARD

Annals of the Rheumatic Diseases

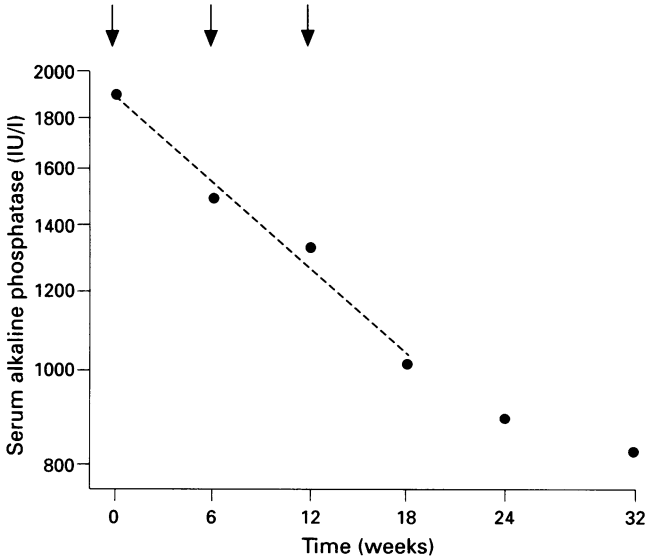
Leaders

Treatment response in Paget's disease

In the past 25 years the calcitonins, and more recently the bisphosphonates, have revolutionised the treatment of Paget's disease such that the nihilistic approach to the management of this disorder that was initially adopted is no longer acceptable. The increasing potency of newer bisphosphonates has shifted the emphasis of treatment, from simply reducing bone turnover, towards the achievement of normal values which are sustained for prolonged periods. The aim of this strategy is to relieve symptoms and to prevent long term complications such as deformity, fracture, and neurological sequelae, though there are no long term studies to confirm the success of these aims. However, peripheral evidence, not least that treatment leads to normal lamellar bone formation rather than the woven bone characteristic of Paget's disease,[1] is supportive of this approach. Although bisphosphonates favourably influence the increased and abnormal bone turnover of Paget's disease, a number of issues remain unresolved. These include how we assess response to bisphosphonate treatment and the determinants of the duration of the response.

Potentially, five parameters could be used to assess response: symptoms, findings at examination, biochemical markers of bone turnover, histological, and radiological features. Of these, the biochemical markers of bone turnover are clearly superior as they are objective, reproducible, readily available, and practical for clinical use. The number of biochemical markers has increased greatly, but though newer markers are fashionable, there is no clear evidence that they are of greater benefit in clinical practice than serum alkaline phosphatase (AP) and urinary hydroxyproline excretion (OHP).[2–5] Of the other parameters, control of symptoms (usually pain) is the primary reason for treatment in most patients, but symptomatic response is subjective and confounded by a 30–40% placebo response.[6] In addition, there are a significant proportion of asymptomatic patients with active disease who may be at risk of developing future complications.[7] Examination is also of limited value in assessing response because, though there may be improvement in deformity[8] and reduction in temperature[9] over affected sites of the skeleton, measurement is difficult and impractical. Repeated bone biopsying is clearly impractical, and though serial changes in plain radiographs[2] and bone scintigraphy with treatment have been evaluated,[10 11] their usefulness in patient management remains unproven. The exception to this is quantitative bone scintigraphy in patients with monostotic Paget's disease.[12]

How can we convey the magnitude of the response of biochemical markers in a meaningful way? For simplicity, I will use AP as an example, though there is evidence that what follows applies equally to OHP.[13] A commonly used method is to express the decrease in AP as a percentage of the preatreatment value (percentage decrease in AP), or the percent decrease of the pretreatment AP in relation to the upper limit of the AP population reference range (percentage decrease of the excess AP).[13–15] Although useful, this is limited by the inverse relationship between these percentage changes and the pretreatment AP, so that the greatest percentage decrease is seen in those with the lowest pretreatment AP.[13] Moreover, the post-treatment AP is also determined by pretreatment AP, so that bone turnover in patients with active disease is less likely to be suppressed into the normal range.[6 16] Therefore, unless matched for pretreatment AP, these methods are not helpful in facilitating comparisons between patients and studies of the efficacy of bisphosphonate compounds. The solution may be the measurement of the rate of decrease in AP with time, which has been shown to be exponential, and easily expressed as a half life on a log-linear plot (figure).[13] Using this method, the half life of AP has been shown to be independent of pretreatment AP[13] (confirming the findings of other studies),[17 18] which would suggest that the half life is a superior expression of response compared with percentage



Change in serum alkaline phosphatase with time for one patient treated with infusions of pamidronate at intervals of six weeks (arrows). Note the long-linear scale. A regression line is shown for the period of treatment and for the first time point after the third infusion. As the effect of pamidronate wears off (24 and 32 weeks), a plateau in the rate of response is evident. From the regression equation the AP half life is calculated to be 21 weeks.[13]

decrease. Also, as there is marked interindividual variation between patients with similar pretreatment AP administered the same dose of intravenous bisphosphonate,[13] the half life of AP seems to give an indication of bone cell sensitivity within an individual. In practice, this may allow identification of good and poor responders early in bisphosphonate treatment, and provide an opportunity to modify therapy in the hope of a better outcome, though prospective studies are required to confirm this.

The ideal outcome of bisphosphonate treatment would be prolonged suppression of bone turnover and decreased complications. The determinants of the duration of biochemical remission have been examined and shown to be dependent on both pre- and post-treatment AP. The greater the AP value, both before and after treatment, the shorter the period during which bone turnover will remain suppressed.[16 18 19] Interestingly, this seems to apply even when the post-treatment AP is within the population reference range,[19] highlighting the difficulties of applying population ranges to individuals. For example, while a post-treatment AP of 100 U/l may be within the population reference range, it may represent a significant increase in bone turnover if that individual's natural AP is 50 U/l. The obvious difficulty is that the natural AP is an unknown quantity, but this observation does suggest that, not only should AP be 'normalised', but the value should be suppressed to well within the population reference range to achieve prolonged remission. Again, prospective studies are required to examine this issue. In addition, the half life of AP seems to be important, in that patients with short half lives to bisphosphonate treatment (presumably the most sensitive) tend to have longer durations of remission.[20]

These observations of the changes in AP with bisphosphonate treatment are in some ways similar to those relating to cancers and cancer chemotherapy. If we assume that Paget's disease is the result of a primary osteoclastic defect (of a as yet undefined aetiology), and that there is a mass of abnormal hypernucleated osteoclasts within the affected skeleton stimulating osteoblastic activity,[21] then the larger the mass the greater the bone turnover and AP; and thus, in patients with a large disease load or high pretreatment AP (analogous to extensive tumour mass), the poorer the outcome of bisphosphonate therapy. In addition, a long AP half life or low sensitivity to bisphosphonate (analogous to tumour resistance to chemotherapy) results in poor outcome and, finally, a high post-treatment AP value (analogous to a large mass of tumour cells after chemotherapy) results in a lower likelihood of prolonged remission. Although simplistic, the final analogy would be that eradication of this abnormal mass of osteoclasts would lead to cure, as occurs when all tumour cells are eradicated in cancer patients. This is the challenge for future drug treatments of Paget's disease.

Departments of Medicine and Rheumatology, SANJEEV PATEL
St George's Hospital,
London SW17 0QT, United Kingdom

1 Kanis J A, ed. Management and assessment of response. In: *Pathophysiology and treatment of Paget's disease of bone.* London: Martin Dunitz, 1991; 225.
2 Hosking D J. Advances in the management of Paget's disease of bone. *Drugs* 1990; **40:** 829–40.
3 Hamdy N A T, Papapoulos S E, Colwell A, *et al.* Urinary collagen cross-link excretion: a better index of bone resorption than hydroxyproline in Paget's disease of bone. *Bone Miner* 1993; **2:** 1–8.
4 Filipponi P, Pedetti M, Beghe F, *et al.* Effects of two different bisphosphonates on Paget's disease of bone: ICTP assessed. *Bone* 1994; **15:** 261–7.
5 Kaddam I M S, Iqbal S J, Holland S, Wong M, Manning D. Comparison of serum osteocalcin and total bone specific alkaline phosphatase and urinary hydroxyproline: creatinine ratio in patients with Paget's disease of bone. *Ann Clin Biochem* 1994; **31:** 327–30.
6 Patel S, Lyons A R, Hosking D J. Drugs used in the treatment of metabolic bone diseases. *Drugs* 1993; **46:** 594–617.
7 Kanis J A, ed. Clinical features and complications. In: *Pathophysiology and treatment of Paget's disease of bone.* London: Martin Dunitz, 1991; 110.
8 Kanis J A, Gray R E S. Long-term follow-up observation on treatment in Paget's disease of bone. *Clin Orthop Rel Res* 1987; **217:** 99–125.
9 Ring E F J, Davies J, Barker J R. Thermographic assessment of calcitonin therapy in Paget's disease. In: Kanis J A, ed. *Bone disease and calcitonin.* Eastbourne: Armour Pharmaceuticals, 1977; 39–48.
10 Ryan P J, Gibson T, Fogelman I. Bone scintigraphy following intravenous pamidronate for Paget's disease of bone. *J Nucl Med* 1992; **33:** 1589–96.
11 Patel U, Gallaher S J, Boyle I T, McKillop J H. Serial bone scans in Paget's disease: development of new lesions, natural variation in lesion intensity and nature of changes seen after treatment. *Nucl Med Commun* 1990; **1:** 747–60.
12 Patel S, Pearson D, Hosking D J. Quantitative bone scintigraphy in the management of monostotic Paget's disease of bone. *Arthritis Rheum.* 1995. In press.
13 Patel S, Coupland C A C, Stone M D, Hosking D J. Comparison of methods of assessing response of Paget's disease to bisphosphonate therapy. *Bone* 1995; **16:** 193–7.
14 Yates A J, Percival R C, Gray R E, *et al.* Intravenous clodronate in the treatment and retreatment of Paget's disease of bone. *Lancet* 1985; **1:** 1474–7.
15 Adami S, Mian M, Gatti P, *et al.* Effects of two oral doses of alendronate in the treatment of Paget's disease of bone. *Bone* 1994; **15:** 415–7.
16 Gray R E S, Yate A J P, Preston C J, *et al.* Duration of effect of oral diphosphonate therapy in Paget's disease of bone. *Q J Med* 1987; **64:** 755–67.
17 Fenton A J, Gutteridge D H, Neil Kent G, *et al.* Intravenous amino-biphosphonate in Paget's disease: clinical, biochemical, histomorphometric and radiological responses. *Clin Endocrinol* 1991; **34:** 197–204.
18 Harinck H I J, Bijoevet O L M, Blanksma H J, Dahlinghaus-Niennhuys P J. Efficacious management with aminobisphosphonate (APD) in Paget's disease of bone. *Clin Orthop Rel Res* 1987; **217:** 79–98.
19 Patel S, Stone M D, Coupland C, Hosking D J. Determinants of remission of Paget's disease of bone. *J Bone Miner Res* 1993; **8:** 1467–73.
20 Patel S. Bisphosphonate treatment of Paget's disease [thesis]. Nottingham: University of Nottingham, 1995.
21 Bone H G, Kleerekoper M. Paget's disease of bone. *J Clin Endocrinol Metab* 1992; **75:** 1179–82.