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CLINICAL CASES

A natural history of bisphosphonate use in Paget's disease of bone

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The discovery and development of bisphosphonates for the treatment of bone disorders depended on early-clinical trials involving patients with Paget's disease of bone (PDB). The patients benefited from these with easing of pain and often a biochemical remission. In turn, the physician–scientists learned more about the mechanism of action of these drugs, translating this into greater potency and safer therapeutic margins in the new-generation bisphosphonates. Mr Raphael has PDB. He has charted his response to bisphosphonates over the past 30 years, his graphs depicting this remarkable history of the evolution of these drugs and their pattern of efficacy.

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Mr Raphael is a 93-year-old American man born to Albanian immigrants in 1922. A first-generation Harvard College graduate, he pursued chemical engineering and worked the last 20 years of his career at Polaroid. At the start of this employment, a required physical examination in 1966 documented an elevated serum alkaline phosphatase (AP) level, and he was determined by radiographs to have Paget's disease of bone (PDB). 'No specific problems were identified,' he reported, and he was not treated. A bone scan showed Paget's disease involving the left femur, proximal right femur, entire pelvis, lower thoracic and upper lumbar vertebral bodies, right scapula and skull.

In 1983, he was admitted to the Massachusetts General Hospital for a porcine valve replacement due to failure of a congenital bicuspid aortic valve. Suspected to have a component of heart failure exacerbated by pagetic bone, calcitonin was administered. This is when Mr Raphael began graphing the treatment of his PDB. The calcitonin 50 IU by injection three times weekly reduced the serum AP by about two-third, a characteristic response to this drug on initial exposure.

Six months later, after the cardiac surgery, he was started on etidronate (ETI/Didronel) 400 mg daily (**Figure 1**). He was prescribed 6 months on the drug, then 6 months off the drug. As charted beautifully by Mr Raphael, the serum AP initially fell a little, then rose when off the medication. Each new set point was a bit higher, and each response less over time. This is often seen with ETI treatment, this waning response to drug. It is unknown whether this is due in part to poor absorption (unlikely to change over time), minimal potency, osteomalacia or other reasons. ETI's mechanism of action differs from the nitrogen-containing bisphosphonates that were to be released in the ensuing years. These newer bisphosphonates were designed to widen the therapeutic margin between inhibition of mineralization and inhibition of osteoclast bone resorption.

In 1988, the units in which the serum AP were measured changed; this is meticulously recorded on his chart. In 1991, while on his fifth cycle of ETI, Mr Raphael was doing some yard work when he suddenly felt pain in his left lower extremity while lifting. He was reluctant to weight-bear due to pain. This is when I initially met him; his physical examination described a focal area of cortical bone tenderness in this limb. There were pseudo-fractures marking the external cortex of bone, and coarsening of trabecular markings consistent with PDB present by radiograph.

In clinical trials and case reports, ETI was shown to worsen lytic lesions in pagetic bone involving the lower extremity and increase the risk of fracture in these patients. ETI is also a cause of drug-induced osteomalacia.[1,2] It is unclear whether impaired bone mineralization may have contributed to the excessive rise in serum AP charted or bone remodeling due to PDB. Mr Raphael was taken off the ETI as noted, and put on crutches, calcium and vitamin D for 6 months. The bone pain resolved, and he resumed weight bearing. He was advised to lift no excessive weights and to avoid any torque to the limb. Then calcitonin was reinstituted as a temporary measure to reduce bone remodeling.

In 1994, a trial of pamidronate (APD) was instituted (**Figure 2**). He received 90 mg, which proved ineffective after the cycles of ETI. This is interesting because APD is often ineffective in a percentage of patients treated with prior bisphosphonates.

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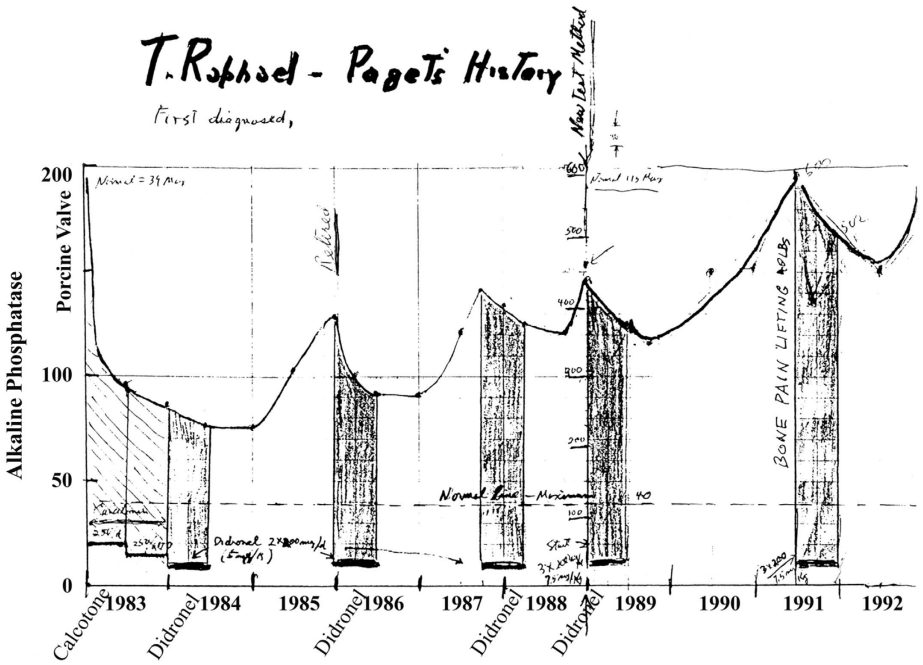

Figure 1 Serum alkaline phosphatase response to treatment (*x* axis) 1983–1992.

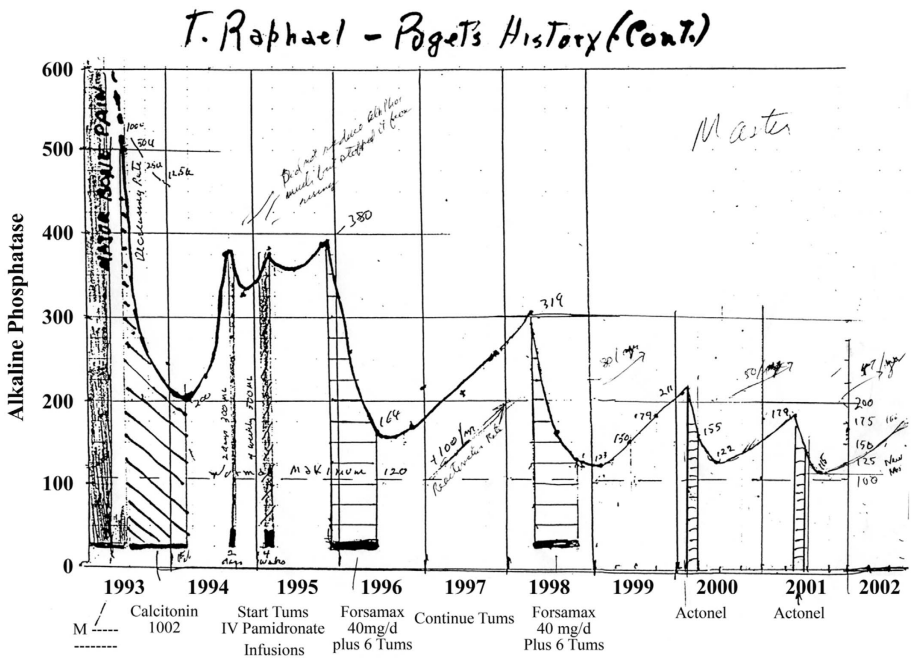

Figure 2 Serum alkaline phosphatase response to treatment (*x* axis) 1993–2002.

The drug also shows loss of efficacy over time in many patients treated with repeated cycles of APD, a phenomenon termed 'pamidronate resistance.'[3] The actual mechanism of APD resistance is not known.

In 1995, he was started on oral alendronate (ALN/Fosamax) 40 mg daily for 6 months (**Figure 2**). The second cycle of this drug almost normalized the serum AP, but with each remission being less sustained than the last. ALN was infrequently prescribed after Food and Drug Administration approval of 35 and 70 mg tablets for the prevention and treatment of osteoporosis in 1997. The 40 mg ALN dose became unavailable in most US pharmacies. The cost for some patients and lengthy forms documenting medical necessity, rather than efficacy *per se*,[4] interfered with access.

Eighteen months later, concerned about a rising serum AP, Mr Raphael started risedronate (RIS/Actonel) 30 mg daily for 2 months (**Figures 2** and **3**). As he completed a second cycle in 2001, his serum AP essentially normalized, and the level remained low with annual cycles of RIS therapy. Sometimes RIS is not that effective in 2 months, following another

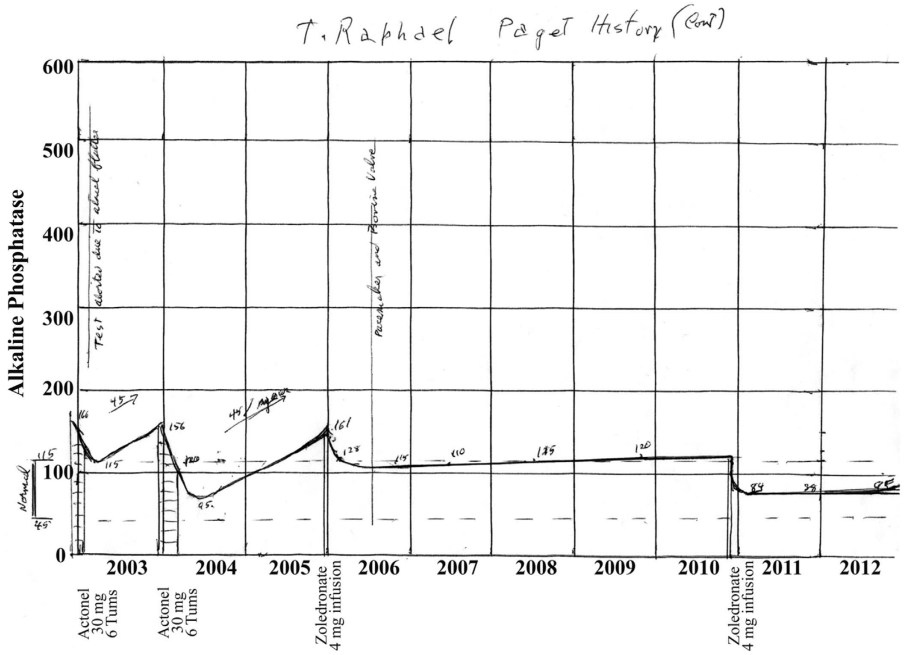

Figure 3 Serum alkaline phosphatase response to treatment (*x* axis) 2003–2012.

bisphosphonate or in patients with extensive polyostotic disease,[5] but he responded beautifully to the drug.

In 2005, hoping for a sustained remission, Mr Raphael received an infusion of zoledronate (ZOL) 5 mg (**Figure 3**). He had an aortic valve replacement with coronary artery by-pass graft the following year (2006), and in 2010 received another cycle of ZOL in anticipation of orthopedic surgery. The efficacy of ZOL in patients naive to bisphosphonates or in those already treated with other bisphosphonates, and the sustained biochemical remission offered by this drug have recommended it as a first-line therapy for patients with PDB now.[6]

Mr Raphael at age 92 underwent a left total knee replacement, attended the Harvard Alumnae 70th Reunion parade last year (2014) and continues to pursue his passion, which is maintaining the network of canals throughout Europe and America. Apart from ETI-induced bone pain and bisphosphonate resistance, he has never had a complication of bisphosphonate therapy, reminding one of the general safety of these drugs in the elderly. Although he has had dental work, he had no teeth extracted. There was no problem healing during orthopedic surgery. He has lost height, suffered compression fractures and evolved spinal stenosis. His bone scan remained active over the years at several sites, even when his biochemical measurements of bone turnover normalized.

His graphs document the remarkable efficacy of the new-generation bisphosphonates, the history of their introduction into US markets, their use, their limitations, and their evolving potency and efficacy in patients with PDB.

Conflict of Interest

The authors declare no conflict of interest.

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