OSTEOPOROSIS SOLUTIONS
"We care about your quality of life"

Assoc Prof Rob Will
BSc (Hons) MB BS FRACP EMBA (UWA)
Physician in Bone and Joint Diseases
Consultant Rheumatologist

Dr Gino Mastaglia
MB BS MRCP (UK)
Consultant Rheumatologist

PHONE: 1300 659 796
FAX: (08) 9472 1082
HEAD OFFICE: 27/443 Albany Hwy
Victoria Park 6100
WEB: www.osteoporosissolutions.com.au
EMAIL: info@osteoporosissolutions.com.au

APPENDIX 8

Benefits and Side-Effects When Bisphosphonates are used to Treat Osteoporosis and Paget's Disease

1. BENEFITS:

The principal benefit of oral bisphosphonate therapy (Alendronate – Fosamax or Fosamax Plus or Risedronate – Actonel or Actonel Combi or ivi Zoledronic acid - Aclastra) is the substantial reduction in all fractures that occur in osteoporotic or osteopenic individuals who are treated with bisphosphonates (1-3). This benefit occurs rapidly and can be detected within six months of commencing therapy. It occurs in patients of all ages and, on average, amounts to about a 50% reduction in the fracture rate. It occurs in patients who had not had a prior osteoporotic fracture and also in patients with a prevalent fracture, either at the spine, hip or peripheral site. This benefit has been observed in older individuals over the age of 70 (2), it has been observed in both males and females and it is likely that this also occurs in younger individuals, though studies have not been undertaken on large numbers, where fracture has been an end point. The benefits of treatment occur in patients who are osteoporotic (T-score $\leq$ -2.5 at the spine or hip) and have not had a prevalent fracture and are also of benefit in patients who are osteopenic (T-score $\leq$ -1 with a prevalent osteoporotic fracture). These agents have also obtained PBS listing now for individuals $\geq$ age 70 with a T-score of $\leq$ -3.0 at any osteoporotic site, determined by DEXA scanning. These criteria were selected as the risk of an osteoporotic fracture rises substantially in older patients with a T score $\leq$ -3.0. A male patient who has a T-score at any site of -3.0 or less has a 10 year risk of hip fracture of 7.8% and of any major site of 16.4%. Conversely, a female with similar results has an absolute risk, over 10 years, of a hip fracture of 8.6% and any osteoporotic fracture of 25.1%. If a female of 70 has had a previous minimal trauma fracture after the age of 50, then her risk of a hip fracture rises to 18.3% and of any fracture of 40% over the next 10 years. These results are derived from the fracture risk calculator (4) now available from the Garvan Institute of Medical Research. This data is based on the Australian Dubbo Osteoporosis Epidemiology Study.

The use of Alendronate, Residronate or Zoledronic acid reduces the absolute risk of fracture in these individuals by about 50%.

There is also substantial data now demonstrating the benefit of oral bisphosphonates in patients commencing or receiving oral corticosteroids (5). There is an increased risk of fracture with daily doses of Prednisolone of 5mg or more at the lumbar spine and at all sites at daily doses of more than 7.5mg.

Another important group of patients who benefit from bisphosphonates are patients with a history of osteogenesis imperfecta (6) and a significant reduction in the rate of fractures has been observed, both in children, teenagers and adults treated for this condition with oral bisphosphonates.

Zoledronic acid has recently been demonstrated to also reduce the rate of all fractures by at least 50% following a once yearly intravenous injection of 5mg, repeated yearly for three years. This drug (Aclastra) has been approved by PBS as a once yearly injection for females who meet standard criteria for bisphosphonate treatment and males if they have sustained a hip fracture.

2. ADVERSE EVENTS:

2.1 Oesophageal and gastric erosions and ulceration

There is substantial evidence from observational studies that bisphosphonates can induce significant oesophageal erosion and ulceration and lead to oesophageal stricture (7). These agents can also lead to gastric and duodenal ulceration and lead to symptomatic abdominal pain, increased reflux, abdominal bloating, weight loss or diarrhoea. In fact, in all patients receiving oral bisphosphonates who develop new gastrointestinal symptoms while taking these medications, these agents should be consider to be a possible reason for these symptoms until found otherwise.

These agents are absolutely contraindicated in patients with achalasia or oesophageal stenosis. They should be used cautiously in patients with a history of reflux oesophagitis. Nevertheless, patients with a history of reflux oesophagitis can be treated with oral bisphosphonates.

2.1.1 Prevention and management of this complication

These side effects can often be avoided by tailoring treatment to the patient. With the availability now of intravenous Zoledronic acid, this agent can be used as an alternative to oral bisphosphonates. Patients could also be treated with Strontium Ranelate as an alternative treatment. Another and common means of preventing these problems is to give patients a PPI inhibitor following their morning bisphosphonate, using a dose of Omeprazole of 20 to 40mg daily or Esomeprazole of 20 to 40mg daily. Alternative PPIs can also be used. Didrocal is a weak bisphosphonate and can be used as an alternative.

2.2 Autoimmune complications

Patients commenced on oral bisphosphonates may develop an increase in joint arthralgias and sometimes this can be quite marked and symptomatic (8). Other causes of a new onset of joint arthralgias or arthritis should be considered but patients receiving oral bisphosphonates should have these agents ceased to see if these symptoms do subside. These symptoms are usually more severe in patients receiving intravenous disodium pamidronate (Aredia) or Zoledronic acid and there can be a marked inflammatory reaction with fevers, rigors and arthralgias. This side effect is no more common in patients with an underlying history of arthritis.

2.2.1 Patients have been reported as having developed uveitis (9) following intravenous bisphosphonates. This rare complication was first reported following intravenous Disodium Pamidronate.

2.3 Osteonecrosis of the jaw

This is a rare complication, which has received a lot of recent publicity, which was misleading (9). This complication is rare in patients who receive oral bisphosphonates for osteoporosis or Paget's disease. This complication refers to necrosis of bone, which can occur either in the maxilla or mandible. It is defined as an area of exposed bone (not covered by mucosal tissue) in the maxilla or mandible that does not heal within 8 weeks of identification. It is felt that this condition occurs due to a combination of marked suppression of bone formation in conjunction with local tissue infection.

Quite extensive studies from Europe have identified a risk of osteonecrosis of the jaw, ranging between 1:10,000 and 1:100,000 patients. This risk is, however, much higher in patients receiving higher doses of these medications for malignancies. The risk in these patients is estimated to be between 1% and 10% of patients. The risk of this complication is high in patients receiving regular glucocorticoids, where there is underlying poor dental hygiene or where an invasive dental procedure has occurred.

The symptoms of osteonecrosis of the jaw include jaw pain, numbness of the jaw and swelling and infection.

2.3.1 Reducing the risk of osteonecrosis of the jaw

This is best done by dealing with any local gingivitis prior to dental treatment in patients receiving oral bisphosphonates. Any symptoms that might be consistent with this condition should be reported to the patient's Dentist. Patients taking bisphosphonates where there is underlying bony metastases or myeloma, should have

a dental evaluation prior to commencing medication. A recent study was published of 7714 women with post menopausal osteoporosis, who received intravenous Zoledronic acid, 5mg or placebo, did not identify any spontaneous reports of ONJ (10). A subsequent independent blind adjudication committee searching the trial's data base identified two patients who satisfied criteria for ONJ. One participant had received placebo and one participant had received Zoledronic acid. Both individuals experienced delayed healing associated with infection and both conditions resolved after antibiotic therapy. The study confirms that ONJ is rare and delayed healing of lesions can occur with or without bisphosphonate therapy.

2.4 Atypical and unusual fractures occurring in patients who have been treated with bisphosphonates

A pattern of bone loss is beginning to be observed in some patients after prolonged use of oral bisphosphonates (11, 12). This generally appears to be after at least 5 years of treatment and it would appear from bone biopsy studies that this is due to excessive suppression of bone formation. The frequency of this complication is unclear. Studies which have followed patients for 5 to 10 years of treatment with oral bisphosphonates suggest that the average patient continues to either maintain or increase their bone mass over this period of time and in one study of Alendronate, the patients who were treated with 10mg daily had a greater increase in bone mass between 5 and 10 years at spine and hips sites compared with those treated with 5mg daily.

Nevertheless, there is a proportion of patients who appear to lose bone and some patients are presenting with unusual fractures, which may be due to inhibition of bone formation as a result of bisphosphonate therapy. There have been reports of subtrochanteric femoral shaft fractures occurring in these patients. There may be other complicating factors, however, including corticosteroid use in these patients.

References: Available on request

Clinical Assoc Prof Rob Will BSc(Hons) MB BS FRACP MBA

February 2009