Bisphosphonates for the Treatment of Osteoporosis

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This review was prepared by the authors in consultation with members of the NSW Therapeutic Assessment Group Inc.
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Executive Summary

The bisphosphonates are a relatively new treatment for osteoporosis. Agents of this family, which have been evaluated for their effect on bone mass include etidronate, alendronate, clodronate, pamidronate, tiludronate, risedronate, ibandronate and zolendronic acid. Bisphosphonates have become a first line treatment for disease that involve excessive osteoclast-mediated bone resorption, such as Paget's disease, hypercalcaemia and tumour-induced osteolysis and osteoporosis

Gastrointestinal intolerance is the most concerning adverse effect of bisphosphonates at doses typically used in osteoporosis.

There are no good studies in relation to pharmacoeconomic analysis
In regard to evidence based therapy in osteoporosis with bisphosphonates the level of evidence is best for alendronate and risedronate in postmenopausal osteoporosis. There is less well established evidence for other bisphosphonates and for other indications.

Decisions regarding treatment for other causes of osteoporosis in women, in men, in children, in corticosteroid induced osteoporosis and after transplantation need to be made with less evidence, without proven antifracture efficacy and by using other endpoints and data in postmenopausal women. Questions regarding optimal dose, comparative efficacy between different bisphosphonates and with other therapies remain. In corticosteroid induced osteoporosis and in men, similar doses and regimens to those established for postmenopausal women can be recommended. In children and post-transplantation osteoporosis it is recommended that treatment should follow protocols established by special interest groups with central collection of data to increase the experience of efficacy and safety.

1. Introduction

Osteoporosis is a disease characterised by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk [1]. Bone mineral density increases from early childhood to a maximum in late teenage years. This 'peak bone density' appears to be determined largely by genetic factors but it is also influenced by environmental and lifestyle factors. With increasing age men and women lose bone gradually: postmenopausal osteoporosis in women results in spine and forearm fractures within 20-25 years of menopause; senile osteoporosis in men and women over 70 years commonly manifests as hip fractures [2].

The World Health Organisation propose diagnostic categories for thresholds of bone density based on the distribution of skeletal mass in young healthy individuals, using T scores. A value equal to the mean is ascribed a T score of zero whereas values two standard deviations above or below the mean would have T scores of +2 and -2, respectively. At a T score of -1 to -2.5 WHO recommend that treatment to prevent bone loss be considered; at a T score of -2.5 or lower WHO strongly advise treatment to prevent further bone loss and fracture [3]. A reduction of at least 2.5 standard deviations, associated with a history of fractures is qualified as severe or established osteoporosis. There is a continuous inverse relationship between bone density and the risk of fracture [3]. Within any age group, one standard deviation fall in bone density multiplies the relative risk of fracture by 1.5 to 2.5 [4]. However the risk of bone fracture cannot be deduced from bone density alone. In assessing individual fracture risk, the presence of symptomatic or asymptomatic fracture will increase the imperative to intervene. In Ross' study of postmenopausal Japanese - American women [5] he found over an average follow up period of 4.7 years, a 5- fold increase in new vertebral fractures in patients with a single vertebral fracture at baseline, a 12-fold increase in risk of vertebral fracture in patients with 2 or more prevalent vertebral fractures at baseline, and a 75-fold increase in vertebral fracture in patients with 2 or more prevalent vertebral fractures at baseline and a BMD in the lowest tertile for the group. Compared with patients with a high bone mass and no history of fracture, patients with one prevalent fracture had, if their bone density was in the highest tertile, a 10- fold increase, and if their BMD was in the lowest tertile a 25-fold increase in vertebral fracture risk.

The bisphosphonates are a relatively new treatment for osteoporosis. Agents of this family, which have been evaluated for their effect on bone mass include etidronate, alendronate, clodronate, pamidronate, tiludronate, risedronate, ibandronate and zolendronic acid. Alendronate, clodronate, tiludronate and etidronate are marketed in Australia in oral formulations and pamidronate is available in parenteral form. The Therapeutic Goods Administration(TGA) has recently recommended risedronate for marketing approval. Alendronate and etidronate (in combination with a calcium supplement) are listed on the Pharmaceutical Benefits Scheme as an authority benefit for *'established postmenopausal osteoporosis in patients with fracture due to minimal trauma. The fracture must have been demonstrated radiologically and the date of the x-ray must be included in the initial application'* and '*established osteoporosis in patients with fracture due to minimal trauma. The fracture must have been demonstrated radiologically and the date of X–ray must be included on the initial application'* respectively.

This paper will review the evidence for use of bisphosphonates in prophylaxis and treatment of osteoporosis, including corticosteroid induced osteoporosis, on behalf of the public hospitals of New South Wales.

2. Bisphosphonates Pharmacology

Bisphosphonates have become a first line treatment for disease that involve excessive osteoclast-mediated bone resorption, such as Paget's disease, hypercalcaemia and tumour-induced osteolysis and osteoporosis. Although bisphosphonates have been used clinically for many years, the exact molecular bases for their antiresorptive effects are only just becoming clear. Bisphosphonates contain two phosphonate groups attached to a single carbon atom, forming a P-C-P structure, and are stable analogues of naturally occurring pyrophosphonate compounds. Bisphosphonates target rapidly to bone mineral in vivo and localise to sites of bone resorption, where they are released and then internalised by resorbing osteoclasts. Bisphosphonates appear to inhibit bone resorption in vivo by directly affecting the function and survival of osteoclasts, although direct or indirect inhibitory effects on osteoclast formation may also be involved.

It appears that bisphosphonates can be grouped into 2 classes with distinct molecular mechanisms of action- those that contain a nitrogen function in the R2 side chain, such as alendronate, pamidronate, zolendronic acid and risedronate and the less potent bisphosphonates that do not contain a nitrogen group, such as clodronate, etidronate and tiludronate. Zolendronic acid is characterised by a side chain consisting of an imidazole ring.This confers a potency two or three orders of magnitude greater than pamidronate [6].
Non- N- bisphosphonates are metabolised intracellularly by osteoclasts to nonhydrolysable analogues of adenosine triphosphate (ATP) which (probably) accumulate to high concentrations and inhibit ATP- dependent enzymes, thereby inhibiting bone resorption and causing osteoclast apoptosis. The N-bisphosphonates are not metabolised, but inhibit the biosynthetic mevalonate pathway, which is required for the prenylation of proteins that play key roles in intracellular signalling pathways that regulate processes fundamental to osteoclast function, including membrane ruffling, trafficking of vesicles, cytoskeletal organisation and also cause osteoclast cell death by apoptosis.[7]

Bone resorption inhibitors such as bisphosphonates are thought to increase bone mass by filling in the 'remodelling' space [8] . Osteoclastic resorption lasts about three weeks and is followed by osteoblastic bone formation which lasts three to four months. This time difference predicts that if resorption is stopped or slowed bone mass will increase for several months while the resorbed space fills in and the emerging resorption space is reduced. The finding that the largest increase in bone mass is produced by bisphosphonates during the first six months of therapy and in bones with the highest rate of remodelling is consistent with this. In addition to the initial rise in bone mass density, some bisphosphonates have been found to continue to increase bone mass for periods up to three years. Several hypotheses have been proposed to explain the increase in bone mass beyond the period necessary for filling of the remodelling space: increase in parathyroid hormone levels caused by small reductions in serum calcium levels; a positive bone balance produced by a longer bone formation period; a higher mineral content; and, direct effects of resorption inhibitors on bone formation [8]. The ability to reduce fracture frequency appears likely to be due to both reduction of activation frequency as well as increased bone density. All bisphosphonates decrease markers of bone turnover and increase BMD over the first few years of treatment.

The bisphosphonates are characterised by low intestinal absorption and highly selective localisation in bone.[7]

3. Clinical Trials

There needs to be a careful weighing of the level of evidence across different studies. The evidence for the newer, better studied bisphosphonates, alendronate and risedronate is greater than for the other bisphosphonates.

3.1 Postmenopausal osteoporosis

3.1.1 Etidronate

In the early clinical trials of etidronate, high daily doses were administered continuously. This was found to impair bone mineralisation [9].

Randomised, placebo controlled trials
Storm et al randomly assigned 66 women to receive etidronate 400mg per day or placebo for two weeks followed by a 13 week period of no drugs for 10 sequences over 150 weeks [10]. Supplementation with calcium and vitamin D was given to both groups for the duration of the study. The primary study endpoints were change in bone mass, progression of vertebral deformity, loss of height and the rate of fracture. The difference between the change in bone mineral content of the vertebra for etidronate compared to placebo was statistically significant 5.3% vs 2.7% (95% CI 2.4-13.6; $p<0.01$). No significant difference between the groups was observed in the rate of new fractures from baseline to week 150 (43 per 100 patient-years for placebo vs 18 per 100 patient-years for etidronate),

however the rate from week 60 to week 150 was significantly better in the etidronate group (54 vs 6 per 100 patient-years; p=0.023).

In a multicentre study, 423 women with postmenopausal osteoporosis were randomised to receive double blind treatment with phosphate 1g or placebo twice daily for 3 days, etidronate 400mg or placebo daily for 14 days and calcium 500mg daily for the remainder of the 91 day treatment cycle [11]. The study was originally designed for two years, extended to three years as a double blind protocol and then to a fourth and fifth year as an open label study.

The primary study endpoints were progression of spinal bone loss and decrease in incidence of vertebral fractures. During the three years of double-blind treatment, spinal bone density increased significantly in the groups that received etidronate with or without phosphate (mean increase 5.08 ± 0.61%) with most of the increase occurring in the first two years. There was no significant change in spinal density in those treated with placebo.. At the end of three years, vertebral fractures were reported in 14.3% of patients (8.6 fractures per 100 patient years) treated with etidronate and 17.4% of patients (11.7 fractures per 100 patient years) not treated with etidronate. This difference was not statistically significant. However, patients who received both phosphate and etidronate had lower fracture rates than those who received placebo and placebo (11.2% vs 21.7%; p<0.05). The open label phase, where all patients received cyclical etidronate treatment, showed that increases in vertebral bone mass and low vertebral fracture rates were maintained [12,13].

Recently, the results of seven continuous years of therapy have been published[14]. One hundred and ninety three patients who completed 5 years of the study continued into a double blind study. The primary efficacy endpoint in this phase of the study was the mean percent change in lumbar spine bone mineral density (BMD) from baseline to weeks 52 and 104. One hundred and sixty six patients(86%) completed the study. The groups receiving cyclical etidronate during this period had statistically significant gains in spinal BMD (increase of 1.8% and 2.2% in 7 and 4 year groups respectively; p<0.05). Miller's study showed that etidronate prevented fractures in those women with low spinal BMD but the fracture rate was too low to demonstrate a significant effect in the entire group.

Randomised, comparative trials

Wimalawansa compared the efficacy of oestrogen with or without etidronate in a four year, prospective, randomised study of 58 early postmenopausal women [15]. Patients received either hormone replacement therapy (HRT) and calcium (n=15), intermittent cyclical etidronate(ICE) and calcium (n=14), HRT, ICE and HRT (n=15) or calcium alone (n=14).The primary study endpoints were change in bone mineral density and development of bone mineralisation defects. The increases in spinal and femoral bone mineral density at four years were 6.78 ± 1.11% and 4.01 ± 0.96% (HRT plus calcium); 6.79 ± 1.31% and 1.20 ± 0.72% (etidronate and calcium); 10.9 ± 1.68% and 7.25 ± 1.59% (HRT plus etidronate plus calcium); and 3.81 ± 0.98% and 4.96 ± 1.15% (calcium alone). The change in bone mineral density was significantly statistically different in patients receiving combination HRT and etidronate therapy compared with either alone. Patients receiving oestrogen and calcium had a significantly greater improvement in femoral bone density than those treated with etidronate and calcium. Histomorphometric measures found that three patients treated with etidronate and calcium had signs of osteomalacia while patients treated with oestrogen (with or without etidronate) had normal histomorphology.

Wimalawansa conducted a further randomised four year prospective study of 72 postmenopausal women to determine whether there is an added beneficial effect on BMD when HRT is combined with cyclical etidronate in patients with established osteoporosis [16]. Patients received either HRT and calcium/ Vitamin D (n=18), intermittent cyclical etidronate and calcium/ Vitamin D (n=18), HRT and etidronate plus calcium/ Vitamin D(n=18), or calcium/Vitamin D alone. Patients in the combined therapy group had an increase in spine BMD of 10.4% ± 0.8 at year 4, and this was a significant increase in comparison with those treated with HRT or etidronate alone (p<0.05). Hip BMD increased by 7.3% in the combined group. The group treated with calcium and vitamin D lost 2.5% (p<0.05) and 4.4% (p<0.01) of BMD in the vertebrae and femora respectively after 4 years.

3.1.2 Alendronate

There are no trials directly comparing the effect of alendronate versus etidronate in reducing the incidence of fractures in postmenopausal women with osteoporosis.

A two year, prospective, randomised, double blind, placebo controlled dose finding study was undertaken in 359 women [17]. Treatment with alendronate 1mg, 2.5mg or 5mg/day or placebo changed lumbar spine bone mineral density on average by 1.21%, 4.10%, 6.23% and 0.56%, respectively. There was also a dose related reduction in the proportion of subjects who suffered vertebral fracture (p<0.05).

A similar three year dose-ranging study of up to 20mg of alendronate in 447 healthy women who had recently experienced menopause [18] showed that total body BMD decreased up to 4% with placebo, was maintained with alendronate 5mg daily and increased significantly only with 10mg of alendronate per day.

Randomised, placebo controlled trials

Nine hundred and ninety four women were randomly allocated to receive placebo or alendronate 5mg daily or 10mg daily for three years or 20mg daily for two years then 5 mg daily for the third year [19]. All patients received calcium 500mg daily. The patients were postmenopausal women (.>5years post menopause) with osteoporosis (spine bone mineral density > 2.5 SD below the mean value in premenstrual white women). The primary study endpoint was change in bone mineral density. Secondary endpoints were rate of fracture, progression of vertebral deformity, height loss and incidence of adverse effects. There were significant increases in the bone mineral density of the spine femoral neck, trochanter and total body at three years in all three alendronate groups and significant losses at all sites in the placebo group. The 10mg dose of alendronate was significantly more effective than the 5mg dose at all skeletal sites and as effective as the 20mg dose. The mean differences in bone mineral density between women taking alendronate 10mg and placebo were 8.8% in the spine, 5.9% in the femoral neck, 7.8% in the trochanter and 2.5% in the total body ($p<0.001$ for all comparisons). The spine deformity index increased 33% in patients on alendronate and 41% in patients on placebo ($p=0.028$). The mean loss of height was 3mm in the patients on alendronate and 4.6mm in patients on placebo ($p=0.005$). New vertebral fractures occurred in 3.2 and 6.2% of women in the alendronate and placebo group, respectively ($p=0.03$). Two further partial reports of this study have been published [20,21].

The Fracture Intervention Trial [22] enrolled 2027 women with osteoporosis with at least one previous vertebral fracture (denoted as vertebral fracture arm). Patients were randomly allocated to receive alendronate 5mg (increased to 10mg at 24 months) or placebo for three years. The primary study endpoint was new vertebral fractures. Follow up x-rays were obtained for 1946 patients. Seventy eight (8%) women in the alendronate group and 145 (15%) women in the placebo group had new vertebral fractures during the study period. This was calculated as a relative risk of 0.53 (95% CI 0.41-0.68).

The clinical fracture arm of the Fracture Intervention Trial [23] aimed to test the hypothesis that 4 years of treatment with alendronate would also reduce the risk of clinical fractures in postmenopausal women who have low BMD but no vertebral fracture. The primary end point was clinical fractures. A total of 4432 women were randomised to receive either placebo or 5mg per day of alendronate for 2 years followed by 10mg per day for the remainder of the trial. Compared with placebo, treatment with alendronate increased average BMD at all measured sites. Clinical fractures occurred in 312 women (14.1%) in the placebo group and 272 (12.3%) in the alendronate group during the study period; a relative risk of 0.86 (95%CI 0.73-1.01). There was not a significant decrease in the risk of clinical fractures in the non osteoporotic women studied, however the study was not designed to pinpoint a threshold for this effect. The effect of more than 4 years of alendronate therapy on fracture risk is not presently known.

Randomised, comparative trials

Treatment with alendronate 10mg or 20mg, placebo or intranasal salmon calcitonin were randomly assigned in a blinded fashion to 286 postmenopausal women with spinal bone mineral density >2 SD below adult mean peak [24]. All patients received supplemental calcium. Results from the one year interim analysis were reported. The percentage change from baseline in bone mineral densities were: spine - minus 0.3% (placebo), 4.4% (alendronate 10mg; $p<0.01$ vs both baseline and placebo), 5.8% (alendronate 20mg; $p<0.01$ vs both baseline and placebo), 0.3% (calcitonin; p=ns); femoral neck - minus 0.2% (placebo), 2.9%(alendronate 10mg; $p<0.01$ vs both baseline and placebo), 2.9% (alendronate 20mg; $p<0.01$ vs both baseline and placebo), 0.3% (calcitonin; p=ns); trochanter - 0.2% (placebo), 3.5% (alendronate 10mg; $p<0.01$ vs both baseline and placebo), 4.0% (alendronate 20mg; $p<0.01$ vs both baseline and placebo), 0.7% (calcitonin; p=ns).

Open label or other studies

Watts et al studied the effect of treatment with alendronate in 25 women with postmenopausal osteoporosis who had failed to respond to intermittent cyclical etidronate (treatment duration 3.3 ± 0.4 years) - as defined by no increase in spine BMD [25]. The primary endpoint was the annualised percent change in spine BMD after treatment with alendronate 10mg daily (1.3 ± 0.1 years), compared with the annualised percent change after therapy with intermittent cyclical etidronate. The changes in BMD after alendronate were significantly higher than after etidronate treatment at all sites - spine 4.4 ± 0.7 vs –1.6 ± 0.6; $p< 0.0001$. Sixteen percent of patients had to discontinue alendronate because of gastrointestinal side effects.

One hundred and twenty postmenopausal women with osteoporosis were randomly assigned to four groups of 30 patients to receive daily either alendronate 10mg, calcitriol 0.5 micrograms, alendronate 10mg plus calcitonin 0.5 micrograms, or calcium 500mg for two years. [26] During the first year the combination of alendronate and calcitriol showed BMD increases in trunk and spine that were significantly higher than for alendronate alone ($p<0.01$).There are now also studies showing efficacy of alendronate in the elderly [27] and Asians [28].
In summary, alendronate studies show that the greatest effect on the fracture rates occurs with a BMD T score < -2.5, especially with a prior fracture.

3.1.3 Clodronate

Sixty women with postmenopausal bone loss were randomly allocated in an unblinded fashion to receive either no treatment (n=20), clodronate oral 400mg daily for 30 days followed by 60 days of no treatment (n=20) or calcitriol 2mcg daily for five days, then clodronate 400mg for 25 days then no treatment for 60 days [29]. Treatment was repeated for 4 cycles over 12 months. The primary study endpoint was change in bone mineral density. The mean changes in spinal bone mineral density at 12 months were -2.34% (no treatment), 3.88% (clodronate; p<0.001 compared with no treatment) and 3.21% (clodronate plus calcitriol; p<0.005 compared with no treatment). Fracture rates were not reported in this study.

Filipponi et al [30] reported on use of cyclical intravenous clodronate (200mg infusion every three weeks) on 235 women with postmenopausal osteoporosis recruited over 6 years. A retrospective cohort of 183 patients was used as control although it is not clear when (which years) these patients were treated. Bone mineral density in the lumbar spine increased by 5.69% in patients treated with clodronate and decreased by 1.47% in controls.

3.1.4 Pamidronate

Reid et al [31] performed a two year, randomised, double blind, placebo controlled trial of oral pamidronate (150 mg per day) in 48 postmenopausal osteoporotic women. Bone mineral density of the total body, lumbar spine, and proximal femur was measured every 6 months by dual energy x-ray absorptionmetry. Bone mineral density increased progressively in the total body (1.9 ± 0.7%; $p < 0.01$), lumbar spine (7.0 ± 1.0%; $p < 0.0001$), and femoral trochanter (5.4 ± 1.3%; $p < 0.001$) in subjects receiving pamidronate, but did not change significantly in those receiving placebo. There were significant decreases in bone density at both the femoral neck ($p < 0.02$) and Ward's triangle ($p < 0.01$) in subjects taking placebo which did not occur in the pamidronate group. The differences between the treatment groups were significant at all sites ($0.0001 < p < 0.05$) except Ward's triangle. Vertebral fracture rates were 13 per 100 patient years in the pamidronate group and 24 per 100 patient years in the placebo group ($p = 0.07$).

Pamidronate 30mg administered as an infusion over one hour every three months (n=16) was compared with daily oral sodium fluoride 20-30mg (n=16) in women with postmenopausal osteoporosis who did not like or could not tolerate hormone replacement therapy [32]. The study was an open, randomised design over two years. The primary study endpoints were changes in bone mineral density and acceptability of treatment. Patients treated with pamidronate had a statistically significant increase in bone mineral density over baseline in the spine (10.1%), femoral neck (4.8%), Wards triangle (4%) and hip region (3.5%). Patients treated with sodium fluoride had a statistically significant increase in bone mineral density over baseline in the spine (12.4%) but the change in all three hip measurements was not statistically significant (± 0.5 to 1.0 %). Side effects occurred in six patients treated with pamidronate and 11 treated with sodium fluoride. No other measures of patient acceptability appeared to have been performed. This group has subsequently reported a retrospective analysis of 132 patients treated with intravenous pamidronate. Of these, 62 women with osteoporosis treated with either 60mg followed by 15mg , 30mg or 60mg every 3 months were followed for 2 years with increase in lumbar spine BMD of around 9% and a non significant increase at the femoral neck. An acute phase reaction occurred in 27% after the first infusion and less frequently after subsequent infusions.[33]

Peretz et al (1996) [34] looked at the efficacy of cyclic pamidronate 30mg infusions in 36 women with postmenopausal osteoporosis. One year effect on calcium metabolism, bone remodelling parameters, and vertebral bone mineral density were investigated. Patients experienced a significant net increase in lumbar spine BMD (0.73 ± 0.04 g/cm[2]vs 0.69 ± 0.03 g/cm[3]; $p = 0.04$) during the first year of treatment; benefits over a longer period are yet to be established.

Gerber (1996) [35] compared 3 doses of intravenous pamidronate in an open study in 44 patients with postmenopausal osteoporosis. The women received either 60mg/15mg (60mg as first infusion, then 15mg), 30mg or 60mg every 3 months; calcium and vitamin D were also given. Lumbar spine BMD increased significantly in all 3 groups: 10% after 60/15 mg, 11% after 30mg and 13% after 60mg.

3.1.5 Risedronate

A double- blind placebo- controlled study was undertaken to determine the effect of oral risedronate therapy on bone loss in healthy early postmenopausal women with normal bone mass [36]. One hundred and eleven women were randomised to receive placebo(n=36), risedronate 5mg daily (n= 37) or risedronate cyclically -5mg daily for the first 2 weeks of each calendar month and placebo daily for the remainder- (n=38) for 2 years followed by one year off treatment. Lumbar spine BMD in both risedronate treatment groups was significantly higher at all time points during the first 2 years compared with placebo ($p <0.05$). Once daily therapy with risedronate 5mg increased bone mass in this patient population- women in this treatment group had significant mean percentage increases in lumbar spine BMD from baseline (1.4%) and vs placebo (5.7%). At the end of the follow-up year, BMD of the lumbar spine and proximal femur had decreased significantly, but were still higher relative to the placebo group, indicating a persistent overall benefit. Risedronate was well tolerated across the two treatment groups.

A 2 year double blind, multi centre study was conducted in Australia to determine the efficacy of risedronate in early postmenopausal women [37]. Three hundred and eighty three subjects were randomly assigned to receive placebo, 2.5mg or 5mg risedronate. All patients received 1000mg of elemental calcium daily. The mean age at baseline was 53 years. Spinal BMD in the 5mg group significantly increased versus baseline and placebo at 3 months the earliest measurement point. Over the 2 year period the difference versus the control group was 4.6%. Significant increases in BMD were also observed at the femoral neck and trochanter with 5mg risedronate as early as 3 months and throughout the study period.

A 2 year double-blind, multicentre, placebo-controlled study was conducted in Europe to evaluate risedronate's efficacy in post-menopausal women with low BMD at baseline (lumbar spine T score below – 2SD). Five hundred and forty one patients were randomly assigned to receive either placebo, risedronate 2.5mg or 5mg; all patients received 1,000mg of elemental calcium daily. The 2.5mg group was discontinued by protocol amendment before the end of the study. At baseline, the mean age was 65 years and the mean spinal T score was –2.9 SD: 29% of patients had prevalent vertebral fractures. Spinal BMD in the 5mg group significantly increase versus baseline (4.1%), whereas the placebo group showed no change over the 2 year period. This increase was significant at the first observation (6 month) time point and throughout the study. The difference in BMD between 5mg risedronate and placebo at the femoral neck and trochanter was 2.3% and 3.3% respectively ($p< 0.05$). The incidence of vertebral deformities showed a trend favourable to risedronate compared with placebo (7% versus 14%) [38].
In two large vertebral fracture trials, one in North America and one in Europe and Australia, risedronate 5mg reduced the incidence of new vertebral fractures by around 50% compared with controls. The European and Australian randomised, double-blind multicentre 3 year study compared the efficacy of risedronate 2.5 or 5mg daily and placebo in reducing the incidence of new vertebral fractures in 1226 women with 2 or more vertebral fractures at baseline. All patients received calcium 1000mg daily and up to 500 IU vitamin D daily if levels were low. The 2.5mg group was discontinued by protocol amendment after two years. At baseline, the mean age was 71 years, the mean time since menopause 24.4 years, the mean lumbar spine T score –2.76 and the median number of prevalent vertebral fractures 3. BMD significantly increased. 7.1% vs 1.3% (lumbar spine), 2.1% vs –1.0% (femoral neck) and 5.1% vs –1.3% (femoral trochanter), the risk of new vertebral fractures was significantly reduced by 49% ($p <0.001$) and the incidence of non-vertebral osteoporosis-related fractures was reduced by 33% ($p= 0.063$) in the 5mg group compared with placebo. [39] In the North American 3 year randomised, double- blind, placebo controlled trial, 2458 ambulatory postmenopausal women younger than 85 years with at least 1 vertebral fracture at baseline were treated with risedronate 2.5 or 5mg daily or placebo. All subjects received calcium 1000mg daily and Vitamin D up to 500 IU if baseline levels of 25-hydrocyvitamin D were low. The 2.5 mg arm was discontinued after one year. Compared with placebo, the 5mg dose decreased the cumulative incidence of new vertebral fractures by 41% (95% confidence interval 18-58%) over 3 years (11.3% vs 16.3%; $p=0.003$). A fracture reduction of 65% (95% CI 38-81%) was observed after the first year (2.4% vs 6.4%; $p< 0.001$). The cumulative incidence of non vertebral fractures over 3 years was reduced by 39% (95% CI 6-61%)(5.2% vs 8.4%;$p=.02$) .Bone mineral density increased significantly compared with placebo at the lumbar spine (5.4% vs .1%), femoral neck (1.6% vs –1.2%), femoral trochanter (3.3% vs –0.7%) and midshaft of the radius (0.2% vs –1.4%). [40]

3.1.6 Ibandronate

A single intravenous bolus dose of ibandronate 1 or 2mg significantly increased lumbar spine BMD in 12 healthy men (by 2%) and five postmenopausal women [41]. Ibandronate (0.25, 0.5, 1 or 2mg) administered as an intravenous bolus dose every 3 months for 1 year resulted in increases in BMD at the spine, total hip and trochanter, but not the femoral neck, in 125 postmenopausal women with osteoporosis [42]. Only the 2mg dose produced significant changes at all sites versus placebo.

3.2 Osteoporosis in men

Several studies have related BMD in men to the risk of fracture [43,44]. However the use of BMD as a basis for therapy in men is not established, and current reference ranges for BMD in men still need to be validated in clinical practice.

Few therapeutic trials have been performed specifically in men, though men with osteoporosis have been included in mixed populations treated with a variety of agents. To date there are no published trials in men using antifracture efficacy as an endpoint.

In addition to the bone loss associated with normal ageing , over 50% of men with symptomatic vertebral crush fractures have secondary causes, which include hypogonadism, alcoholism, corticosteroid use long term, parathyroid disorders and transplantation. [45]

In a small uncontrolled study of men with idiopathic osteoporosis manifested as vertebral fractures [46] intermittent cyclical etidronate (ICE) significantly increased spinal BMD by 3.2% versus baseline over 2 years. A significant

increase in spinal BMD (6% over 2 years) was also obtained with ICE in 44 men with idiopathic or secondary osteoporosis. [47]

Randomised controlled trials enrolling only men are needed to confirm these results.

3.3 Corticosteroid-induced osteoporosis

Adachi et al [48] studied use of intermittent etidronate therapy to prevent corticosteroid induced osteoporosis. One hundred and forty one men and women who had recently commenced high dose corticosteroids were randomly assigned to receive etidronate 400mg or placebo daily for 14 days, followed by calcium 500mg for 76 days. The primary outcome measure was the change in bone mineral density of the lumbar spine from baseline to week 52.

The mean change in the etidronate treated group was +0.61 ± 0.54% compared with -3.23 ± 0.60% in the placebo treated group (p=0.02). The result was significantly different for the stratified groups of premenopausal women (n=15; p=0.02) and post menopausal women (n=60; p=0.001) but not men (n=31; p=0.07). Ten patients in the placebo group (15%) and 5 ((9%) in the etidronate group had a total of 27 new vertebral fractures during the study. The relative risk of fractures in the etidronate group was 0.6 (95% CI 0.2-1.6; p=ns).
Roux et al undertook a prospective, double blind, multicentre study of the efficacy of intermittent etidronate therapy on lumbar spine BMD changes in patients initiating high-dose corticosteroid therapy [49].One hundred and seventeen patients (45 men and 72 women) were randomly assigned oral etidronate 400mg /day or placebo, for 14 days followed by 76 days of elemental calcium 500mg, cycled over 12 months. Corticosteroid treatment had to be expected to continue for at least 12 months with the initial 90 days at a mean dose of at least 7.5mg prednisone. After one year, the mean difference between groups, ie the treatment effect, was 3.0 ± 0.84%; p=0.004 confidence interval 1.18-4.80)

Alendronate has been studied in the prevention and treatment of corticosteroid- induced osteoporosis in men and women Two multicentre double-blind studies involved 560men and women who were receiving long term, prednisone 7.5mg or equivalent [50]. Patients were randomised to receive alendronate 5mg daily (n= 161), alendronate 10mg daily (n= 157) or placebo (n=159) for 48 weeks. After four years of therapy alendronate 5mg and 10mg significantly increased spine BMD compared with placebo and baseline. Alendronate 10mg significantly increased spine BMD compared with 5mg dosage in postmenopausal women.
Boutsen et al [51,52,53] conducted studies in patients commencing glucocorticoids, and report on the efficacy of pamidronate, coadministered with oral calcium supplements in achieving primary prevention of glucocorticoid induced osteoporosis maintaining BMD at lumbar spine and femoral neck. Boutsen 1997 [52], studied 27 patients requiring first time corticosteroid therapy (at least 10mg prednisone equivalent). Patients were randomly selected to receive concomitantly with onset of high dose steroid therapy, either pamidronate and calcium or pamidronate alone. Pamidronate dose was initially 90mg IV, followed by 30mg IV every 3 months whilst on steroid therapy. BMD increased significantly at lumbar spine (3.6%) and femoral neck (2.2%) in the pamidronate group causing the authors to conclude that early administration of intravenous pamidronate effectively protects against the rapid bone loss during the first months of glucocorticoid therapy. Boutsen 1998 [53], compared efficacy of 2 dosage regimens of IV pamidronate: 10 patients received a single IV 90mg infusion, a second group of 10 patients received firstly 90mg IV pamidronate and subsequently 30mg IV every 3 months. At one year, no difference in lumbar spine and hip BMD measurements was observed between pamidronate regimens, but a highly significant difference was observed between both the pamidronate regimens and controls

In a 12 month open randomised prospective study, Charlwood et al [54] compared intermittent 30mg pamidronate infusions with salcatonin and cyclical etidronate in 60 patients with steroid induced osteoporosis (secondary prevention). At one year lumbar spine BMD in patients treated with pamidronate increased significantly from baseline 0.873 ± 0.156 to 0.915 ± 0.171 ; p = 0.0001). Etidronate 400mg daily for 2 weeks in every 12 produced the greatest increase in lumbar spine BMD (0.864 ± 0.134 to 0.958 ± 0.132; p+0.004).
In a trial of prednisolone recipients treated for over 5 years for respiratory or collagen vascular disease, pamidronate and calcium increased spine BMD by 19.6% compared to a decrease of 8.8% in those who received calcium alone. [55]

3.4 Osteoporosis in children

Brumsen et al [56] reported a series of 12 cases of pamidronate or olpadronate use in children with osteoporotic disease: idiopathic osteoporosis (n=6); osteogenesis imperfecta (n=4), juvenile arthritis (n=1) and mitochondrial disorder (n=1). Ten children were treated with intravenous and/or oral pamidronate and two were treated with olpadronate. Bone mineral density improved in all patients, particularly those treated prior to puberty. Patients treated before or in early puberty demonstrated catch up growth while those treated in late puberty showed no growth. Patients generally became more mobile and the rate of fracture fell in patients with osteogenesis imperfecta.

The bisphosphonate research group at New Children's Hospital, Sydney NSW, has gained considerable experience in the use of pamidronate in children. In 1994 a trial of cyclic intravenous pamidronate was commenced in children with osteogenesis imperfecta (OI)-a heterogeneous group of disorders with at least 12 phenotypes recognised at present; the bone fragility is complicated by both an age related osteoporosis and by immobilisation osteoporosis. At present 42 children are enrolled in this trial and receive 30mg/m^2 monthly or second monthly. In 6 of 11 patients with Type 1 OI treated for at least 12 months, a significant increase in total body and femoral neck and non significant increase in lumbar spine bone density was seen. In 11 of 18 patients with Type IV OI, a significant increase in spinal and a non significant increase in total body and femoral neck BMD was seen.[57,58]

3.5 Transplantation

As survival improves with new surgical and immunosuppressive treatments, bone disease following organ transplantation is increasingly becoming a cause of serious morbidity.

3.5.1 Lung Transplantation

Lester et al [59] evaluated the efficacy of pamidronate plus vitamin D and calcium, versus vitamin D and calcium alone, in preventing the development of osteoporosis in a 2 year randomised controlled trial in cystic fibrosis patients following lung transplantation. A total of 34 patients were studied, and 21 completed the 2 year trial period. An IV infusion of 30mg pamidronate was administered every 3months for 2 years. The vitamin D dosage was 800IU daily and calcium dosage was 1g daily. Compared to the vitamin D and calcium supplementation alone arm, the pamidronate group had significantly greater increases in spine ($p = 0.003$) and femur ($p = 0.01$) BMD after 2 years. Four non-vertebral fractures occurred in the vitamin plus calcium alone group, versus 2 in the pamidronate patients. The groups did not differ regarding degree of immunosuppression. No mention is made of adverse events. The authors concluded that the data suggests that pamidronate is an effective agent for osteoporosis in cystic fibrosis patients after lung transplantation.

3.5.2 Liver Transplantation

Two articles discuss the use of pamidronate in patients who have are about to receive or have received a liver transplant. Russo Picasso et al [60] present the results of a study in a conference abstract. This study included 37 patients awaiting a liver transplant and they were randomised to placebo (n=11), intranasal calcitonin (200 U daily, n=18), or oral pamidronate (oral pamidronate; 200 mg daily; 8 patients) during the first year after transplantation. Patients also received ergocalciferol (25000 U per week) and elemental calcium (1 g daily). The authors concluded that pamidronate plus ergocalciferol and calcium was more effective in preventing bone loss at the lumbar spine during the first 3 months after transplantation than either calcitonin plus ergocalciferol and calcium, or ergocalciferol and calcium alone. Bone loss at 3 months after liver transplantation might be mediated by parathyroid hormone.
Reeves et al [61] investigated the ability of pre-operative BMD to predict the incidence of osteoporotic vertebral fractures following liver transplantation, and of IV pamidronate to prevent fractures. The study included 13 high-risk patients who were treated with 60 mg IV pamidronate every 3 months prior to surgery and for 9 months post-operatively. Immunosuppressants used were cyclosporin, azathioprine, prednisolone, methylprednisolone and tacrolimus, and calcium supplements and vitamin D were also given to jaundiced patients.
The authors concluded that a low lumbar spine BMD is associated with a high risk of symptomatic vertebral fracture after liver transplantation and the results of the study suggest that this risk is considerably reduced by the administration of IV bisphosphonate before and after transplantation.

3.5.3 Heart Transplantation

An abstract by Krieg et al [62] describes a study of IV pamidronate in post-transplantation osteoporosis. Eight men received prednisone, cyclosporin (mean dosage 306 mg daily), calcium (1 g daily) and vitamin D (1000 U/daily). BMD was measured at heart transplantation, at the onset of treatment, and then every 6 months. Intravenous pamidronate (60 mg every 3 months) was started at a mean of 8 months after transplantation. A 3 year treatment with IV pamidronate after heart transplantation was reported to increase bone mass at the lumbar spine and prevent osteoporosis at the proximal femur.

Shane et al [63] carried out a pilot study that investigated the effects of IV pamidronate followed by oral etidronate on bone loss induced by glucocorticoids and cyclosporin in 18 patients during the first year after heart transplantation. Pamidronate was administered as a single IV 60 mg infusion, approximately 9 days after heart transplantation. The authors concluded that heart transplant recipients treated with bisphosphonates and replacement doses of calcitriol sustained less bone loss and fewer fractures that those treated with calcium and vitamin D only. Bisphosphonate therapy, in conjunction with calcitriol, shows promise for the prevention of transplantation-related osteoporosis.

3.6 Other

A cohort study examined the effects of cyclical etidronate when used in routine clinical practice, on the prevention of fracture [64]. Information was obtained from the General Practice Research Database (UK);a total of 7977 patients taking cyclical etidronate treatment and an equal number of matched control patients with a diagnosis of osteoporosis were analysed. Those taking cyclical etidronate had a significantly reduced risk of hip fracture (by 34%) relative to the osteoporosis controls [relative risk = 0.66; 95% CI 0.51-0.85]. Within the etidronate cohort, the incidence of non vertebral and vertebral fractures decreased significantly over time (4.3% at Year 1, 2.9% Year 3 or later). Fracture incidence in control group remained stable. When fracture incidence rates were compared between the two groups the rate of non vertebral, hip and wrist fracture decreased significantly ($p< 0.05$) with increasing etidronate exposure.

One hundred and seven patients were randomly assigned to short term treatment (three doses at weekly intervals) with clodronate (150mg, 300mg, 600mg), etidronate 300mg or placebo given as intravenous infusions [65]. The changes in spinal bone mineral density at 24 months were -2.5% (placebo), -2.7% (clodronate 150mg), -1.7% (clodronate 300mg), -3.1% (clodronate 600mg), -0.4% (etidronate 400mg).
Risedronate has been extensively studied in a large clinical trial program involving approximately 16,000 patients world-wide. The Phase III studies have encompassed a wide variety of patients including early postmenopausal females, postmenopausal women with established osteoporosis and male and female patients taking corticosteroids.

Pamidronate has also been used for several other indications including reducing bone pain associated with advanced osteoporosis [66], chronic back pain with senile or glucocorticoid induced osteoporosis [67] and spinal pain caused by osteoporosis secondary to systemic mastocytosis [68].

3.7 Meta Analyses

Homik *et al* performed a meta analysis of 13 trials including 842 patients to evaluate the efficacy of bisphosphonates in corticosteroid–induced osteoporosis [69]. The primary outcome assessed and required for inclusion was percent change in BMD at one year at the lumbar spine or femoral neck. Most trials used cyclical etidronate; there was one trial each with daily etidronate, oral risedronate, oral alendronate and daily oral pamidronate. Only four trials reported fracture data. There was a weighted mean difference of 4.3% (95%CI 2.7-5.9) between treatment and placebo groups in lumbar spine BMD at 12 months (ie on average the treatment and placebo groups had a percent change in bone density that differed by four percentage points). The authors concluded that bisphosphonates appear to be efficacious at preventing and treating corticosteroid- induced bone mineral loss at the lumbar spine; however long term efficacy (over 12 months) and efficacy against spinal fractures cannot be adequately established.

A meta-analysis of five randomised controlled double blind studies trials of at least two years duration was prepared by Merck Research [70]. It was conducted because it was believed that the individual studies did not have sufficient power to detect a sufficient difference in the overall incidence of non vertebral fractures. Patient data from treatment arms that used alendronate 1mg were excluded although other patient data from these studies was included. Data were analysed using an intention-to-treat approach. Nonvertebral fractures were reported in 60 of 590 patients (10.2%) in the placebo group (4.45 women with nonvertebral fractures per 100 patient years) compared with 73 of 1012 patients (7.2%) in the alendronate group (3.26 women with non vertebral fractures per 100 patient years. The relative risk for nonvertebral fractures was 0.71 (95%CI 0.502-0.997; p=0.048) with alendronate therapy compared with placebo.

Macedo et al [71] compared the effects of three groups of antiresorptive drugs in post menopausal osteoporosis: oestrogens and placebo, calcitonins and placebo and bisphosphonates and placebo. Relative to placebo the global effect sizes were: bisphosphonates 0.87(CI 95% 0.68-1.07; p<0.00001), oestrogens 0.54 (CI 95% 0.34-0.73, p<0.00001) andcalcitonins 0.41 (CI 95% 0.21-0.61, p<0.00001) . The meta analysis thus indicate that bisphosphonates exert a greater effect on spinal bone mass in women during the postmenopausal period compared with oestrogen replacement and calcitonin.

Cardona and Pastor [72] undertook a meta-analysis of 24 randomised controlled trials that examined the effectiveness of calcitonin (n=18) or etidronate (n=6) in the treatment of postmenopausal osteoporosis. Another 21 studies were excluded from the meta-analysis because combination therapies were used (other than vitamin D and calcium), no control group was included, randomisation was not declared, vertebral fractures were not reported or the study was reported in both preliminary and final stages. The pooled differences in incidence of fractures were 59.2 fractures per 1000 patient years (95% CI 55.1-63.3) for calcitonin and 28.3 fractures per 1000 patient years (95% CI 26.2-30.4) for etidronate. The change in vertebral bone mineral density in trials with an above average quality score was 1.77% (95% CI 1.54-2.0) for calcitonin and 3.12 (95% CI 2.84-3.40) for etidronate; the respective changes for primary prevention were 2.2% (95% CI 2.0-2.4) vs 6.9% (95% CI 6.2-9.6) and 0.9% (95% CI 0.4-1.4) vs 3.1% (95% CI 2.8-3.4).

4 ADVERSE EFFECTS

Early studies found that doses of etidronate above 800mg per day impaired normal skeletal mineralisation and this may be associated with the appearance of fractures. However at the doses used in the treatment of osteoporosis, the bisphosphonates do not induce clinical or histological signs of impaired mineralisation.

Treatment initiation, particularly with high doses or intravenous administration of bisphosphonates has been associated with flu like symptoms and fever for one to three days which may be associated with transient haematological changes resembling a typical acute phase response [73].

Gastrointestinal intolerance is the most concerning adverse effect of bisphosphonates at doses typically used in osteoporosis. A review of all reports to the manufacturer as of March 1996, found that alendronate had been prescribed for an estimated 475,000 patients for 1213 reports of adverse effects of which 199 related to the oesophagus [74]. Endoscopic findings usually showed chemical oesophagitis with erosions or ulcerations and exudative inflammation. Swallowing the tablets with adequate water and remaining upright for at least 30 minutes thereafter have been recommended as means of avoiding oesophageal ulceration.

The most commonly reported adverse events in the double blind, placebo controlled trials of etidronate were: back pain (etidronate 16.2% vs placebo 18.4%), flu syndrome (12.2% vs 11.8%), nausea, dyspepsia and diarrhoea (12.2% vs 22.4%) [13]; asthenia (22.2% vs 29.6%), pain (18.5% vs 18.5%), flu syndrome (18.5% vs 14.8%), nausea (14.8% vs 11.1%), abdominal pain (14.7% vs 3.7%), dyspepsia (11.1% vs 7.4%) and constipation (11.1% vs 0).

The most commonly reported adverse events in the major double blind placebo controlled trial of alendronate were: abdominal pain (alendronate 6.6% vs placebo 4.8%), musculoskeletal pain (4.1% vs 2.5%), nausea (3.6% vs 4%), dyspepsia (3.6% vs 3.5%), constipation (3.1% vs 1.8%), diarrhoea (3.1% vs 1.8%) [18]

The safety profile of risedronate 2.5 and 5mg daily has now been studied in 5226 postmenopausal women in placebo-controlled trials of up to 3 year's duration. These subjects were not excluded on the basis of underlying history of GI disorder or NSAID use. The proportion of patients reporting adverse events or withdrawing due to adverse events was similar in the 5mg and placebo groups. Patients reporting moderate to severe upper GI adverse events underwent endoscopy at the discretion of the investigator-68 from the 5mg group and 69 from the placebo Group. The number of patients with oesophageal ulcers on endoscopy was 7 in the 5mg group and 11 in the placebo group. There were a comparable number of gastric ulcers between groups. While the number of patients with inflammation in the duodenum was higher in the 5mg group compared to placebo (8 vs 2) the number of patients with duodenal ulcers was higher in the placebo group (7 vs 2). When corrected for different exposures, the adverse event profile of 2.5mg was generally similar to that of 5mg [75].

Studies in Europe and North America have been conducted to determine the efficacy and safety of risedronate in the prevention and treatment of corticosteroid-induced osteoporosis. In the prevention study, patients had corticosteroids initiated within 3 months of enrolment whereas patients in the treatment study had been on corticosteroids for an average of 5 years prior to enrolment.. Risedronate was well tolerated with adverse events similar across groups. [76]

5 ECONOMIC CONSIDERATIONS

There are no good studies in relation to pharmacoeconomic analysis. Australian data from the prospective Dubbo Osteoporosis Epidemiology Study suggest that 56% of women and 29% of men over the age of 60 years will sustain an osteoporotic fracture in their lifetime. Hip fractures comprise about 20% of these, with other common sites being forearm (19%), humerus (11%), ribs (12%) and lower leg (19%) [2]. Early mortality associated with hip fractures ranges from 20-50%, and about 50% of hip-fracture survivors are discharged to nursing homes because of poor mobility and inability to cope with activities of daily living [2].

The Geelong Osteoporosis Study [77] identified fractures in people aged 35 years and over. During the two year ascertainment period, 2184 adults sustained fractures, producing an age and sex adjusted incidence of 102 per 10,000 person-years. The number of fractures per year is projected to increase 25% from 1996 to 2006 (83,000 to 104,000). The authors estimated that hip fracture alone accounted for 0.9% of total government health services expenditure for 1995/6.

The consequences of osteoporosis are costly both in terms of lives and resource utilisation. The predicted annual treatment costs in Australia for atraumatic fractures in over 60 year olds were estimated at $44million per million population in 1995 [4]. This was prior to the widespread availability of preventative treatment with bisphosphonate compounds.

The current cost of bisphosphonates to NSW hospitals is:

Etidronate	(Didronel)	400mg for 14 days every 90 days plus the cost of calcium supplementation	- $183 p.a.
	OR		
	(Didrocal)	3 month pack $71.67	ie $287 p.a.
Alendronate		10mg daily	-$635 p.a
Pamidronate	(Aredia)	15mg, 4 units 90mg, 1 unit	$263.99 $387.03

Chrischilles et al [78] have presented preliminary results of the Fracture Intervention Trial (FIT) Healthcare Utilisation Substudy which evaluated the effects of alendronate versus placebo on fracture- related health care utilisation and costs. Data were obtained from the Vertebral Fracture arm of the FIT [22]**.** For each patient who experienced a clinical fracture the study assessed whether treatment was provided in an emergency room, hospital, nursing home and /or rehabilitation hospital as a consequence of the fracture. Alendronate significantly reduced the percentage of patients using any fracture- related health care versus placebo,by 25% (8.1% vs 10.8%;p= 0.038 95%CI 0.4%, 5.2%) .

Buckley [79] estimated the cost-effectiveness of calcium and vitamin D supplements versus alendronate alone for the prevention of corticosteroid–induced osteoporosis based on data from published clinical trials. A decision analysis model was used to estimate the number of patients who would develop osteoporosis after 2 years of steroid therapy. (The authors assumed all patients were taking oestrogen replacement therapy). The cost of preventing osteoporosis in patients with borderline osteopenia (T score = -1) using alendronate compared to calcium and vitamin D supplements was $18,275 US per additional episode prevented at 2 years. In women with moderate osteopenia (T score = -1.5) the cost was around $3,5000 per episode prevented. The authors concluded that the cost–effectiveness of alendronate increased significantly when used in osteopenic patients at a greater risk for corticosteroid–induced osteoporosis. The less costly regimens such as calcium and vitamin D may be more cost effective in patients with normal BMD at the commencement of corticosteroid therapy.

Homik et al [80] presented preliminary results of a cost effectiveness study evaluating 3 strategies for prevention of corticosteroid-induced osteoporosis in young women. Prevalence rates for osteopenia and fractures were obtained from the literature and efficacy of bisphosphonates determined by meta analysis of published clinical trials. Costs were calculated from Canadian government data, and published sources. The model assumed five years of glucocorticoid therapy and another five years of follow up. Cost effectiveness ratios were most favourable for preventing vertebral fractures (due to their high prevalence). Hip fracture prevention was more costly because of low incidence in study population.

	Expected Cost Per patient	Risk of Vertebral Fracture	Risk of hip fracture	Cost to prevent a Vertebral Fracture*	Cost to prevent a Hip Fracture*
No prophylaxis -	$75	100/1000	5/1000	-	-
Conventional prophylaxis -	$170	60/1000	4/1000	$2000	$90,000
Universal prophylaxis -	$780	20/1000	3/1000	$9000	$50,000

**compared to no prophylaxis*

Hip fractures invariably require hospitalisation and frequently permanent institutionalisation or disability or both [81]. Although vertebral fractures typically result in lower economic costs than hip fractures, the associated disability, pain and emotional distress can have significant negative impact on the patients quality of life. [82]

6 Recommendations

6.1 Postmenopausal osteoporosis

In regard to evidence based therapeutic utilisation in postmenopausal osteoporosis, the level of evidence is best for alendronate and risedronate, as both bisphosphonates have been subjected to large-scale double blind randomised clinical trials. Risedronate has received FDA and European approval for the treatment and prevention of post menopausal osteoporosis and for the prevention and treatment of corticosteroid induced osteoporosis.

There is much less evidence of efficacy for cyclical etidronate or pamidronate, which have only been studied in small double blind randomised trials, and the level of evidence is comparable with or better than the level of evidence of efficacy of calcitriol. The main trials of etidronate are flawed by post hoc unplanned subgroup analyses, but these trials and those of pamidronate support a class effect of bisphosphonates and the efficacy of all four in postmenopausal osteoporosis. New large well-designed clinical trails with cyclical etidronate or pamidronate are unlikely to ever be performed.

The NSW Therapeutic Assessment Group believes there is evidence to support the prevention and treatment of osteoporosis with all four agents

- cyclical intermittent etidronate in combination with calcium supplementation
- alendronate 10mg daily
- pamidronate 30mg intravenously 3 monthly
- risedronate 5mg daily

At present alendronate should be considered for first line treatment, followed by cyclical etidronate or pamidronate (choice between these two based on feasibility of oral versus IV dosing and expense involved at individual institutions). Risedronate was approved by ADEC for marketing in Australia in April 2000.

However the optimal dose, duration of therapy and comparative efficacy between bisphosphonates and hormone replacement regimens is yet to be established.

6.2 Corticosteroid induced osteoporosis

The level of evidence of efficacy of bisphosphonates here is less than with postmenopausal osteoporosis. Meta analysis of the numerous small studies with alendronate and risedronate indicate efficacy. The National Osteoporosis Society in the United Kingdom recently recommended the use of bisphosphonates for the prevention of bone loss in patients receiving high dose corticosteroids and as a treatment option in those patients who have already developed fractures.The same bisphosphonate regimens are appropriate in the prevention and treatment of steroid induced osteoporosis.The same questions remain regarding comparative efficacy between bisphosphonates and with calcitriol, oestrogen and selective oestrogen-receptor modulators.

6.3 Osteoporosis in men

Whilst there is a need for the results of large double-blind randomised trials in men with fracture endpoints, current data supports an expectation of efficacy. Decisions are made using data in women and limited data with endpoints such as BMD, bone turnover markers etc. As bone loss proceeds by reduced formation and trabecular thinning rather than perforation response to therapy may be different in men than women. At the present time doses and regimens similar to those used in women can be recommended.

6.4 Osteoporosis in children

Early trials show evidence of efficacy in children particularly in OI. Use can be recommended but should follow protocols established by interest groups such as the bisphosphonate research group at the New Children's Hospital, and the data collected centrally to increase our experience of its efficacy and safety in children.

6.5 Transplantation

Limited data supports efficacy, and bisphosphonate use should follow protocols established by interest groups wherever possible with central collection of data to build up evidence of efficacy.

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