

Osteoporosis in the very elderly

Osteoporosis management in older people should be aimed at fracture prevention. Most trial evidence involving anti-osteoporotic medications in reducing fragility fractures exists in women up to the age of 80 years. In this review we discuss the management of osteoporosis in the very elderly, those over the age of 80, focusing on the evidence for anti-resorptive and anabolic agents in reducing fragility fractures in this particular age group.

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Fractures and their sequelae are the main outcomes of osteoporosis, and hip fractures in particular are associated with significant morbidity and mortality. Fractures increase exponentially with age and it is estimated that 30% of all fragility fractures occur over the age of 80 years. Moreover, the majority of hip fractures occur in women over the age of 75 years. Patients over the age of 80 years are often denied osteoporotic treatments because it might be felt that the treatments do not work or they are "too late to treat". In this article, we look at what is currently licensed for the treatment of osteoporosis with evidence of efficacy in the over 80 years age group with particular regard to fracture reduction. Vitamin D, calcium and hormone replacement therapy were not included in this particular review.

Methods

A literature search was performed to look for randomised controlled trials (RCTs) and systematic reviews using sources including Pubmed, EMBASE and CINAHL. Key Mesh terms included "aged", "frail elderly", "aged 80 and over" and "geriatrics". A review of published abstracts presented in the last 2 years at international meetings relevant to osteoporosis was also performed. Search results were sifted to include articles involving antiresorptive and anabolic agents (licensed for osteoporosis) which included subjects aged 80 years and over.

Bisphosphonates

The evidence that currently exists for bisphosphonates in reducing fracture outcomes in patients over the

age of 80 years is available only for risedronate and zoledronate. Trials involving etidronate, alendronate and ibandronate only included a small number of subjects over the age of 80 years.

In terms of risedronate, the evidence base for this age group stems from the Vertebral Efficacy with Risedronate Therapy—Multinational (VERT-MN), VERT-North America (NA) and the Hip Intervention Program (HIP) where a pooled analysis by Boonen et al from these three randomised controlled trials (RCTs) involving just under 1400 patients over the age of 80 showed a 81% reduction in new vertebral fractures at 1 year (95% CI 60%–91%) and a 44% reduction at the end of 3 years (95% CI 19%–61%).^{1–4}

In the HIP study, McClung et al showed a significant 40% reduction in hip fractures in the 70–79 age group. However in the 80 years and over group where patients were selected on the basis of non-skeletal risk factors, no significant reduction in hip fractures were seen. In the combined intention to treat (ITT) population (age 70–100 years) a significant 30% hip fracture risk reduction was seen (95% CI 10%–40%).¹ In a post hoc analysis of the HIP study, those women aged 70–100 years with established osteoporosis (femoral neck NHANES BMD < -2.5 SD and at least one prior vertebral fracture) had a 46% reduced risk of hip fracture at 3 years (95% CI 9%–68%).⁵

With regards to zoledronate, the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial (PFT) and HORIZON Recurrent Fracture Trial (RFT) included approximately 900 patients aged 80 years and above for their studies. In HORIZON PFT (patients aged 65–

89 years), there was a significant 70% reduction in morphometric vertebral fractures at 3 years (relative risk 0.30 95% CI 0.24–0.38), with reductions at 1 and 2 years at 60% and 71% respectively. In terms of the incidence of new hip fractures, a significant 41% reduction was seen (hazard ratio, 0.59; 95% CI 0.42–0.83). All non-vertebral, clinical, and clinical vertebral fractures were also significantly reduced by 25%, 33% and 77% respectively ($p < 0.001$ for all comparisons).⁶ In HORIZON RFT, zoledronate was associated with a 28% relative reduction in risk of death compared with placebo ($p = 0.01$).⁷ There were no published subgroup analyses performed as yet looking at how the over 80s performed in these two trials.

Strontium ranelate

There have been two trials involving the use of strontium ranelate: the Spinal Osteoporosis Therapeutic Intervention study (SOTI) and the Treatment Of Postmenopausal Osteoporosis study (TROPOS).^{8,9} The SOTI study showed a significant 49% reduction in new vertebral fractures at 1 year in the treatment group (95% CI 26%–64%) and a 41% reduction over 3 years (95% CI 27%–52%).⁸ The TROPOS study showed that in the ITT population there was a significant 16% reduction in all non-vertebral fractures over 3 years with strontium ranelate (95% CI 1%–30%). Subgroup analyses showed that the risks of major non-vertebral fractures (hip, wrist, pelvis, sacrum, ribs, sternum, clavicle, humerus) were reduced by 19% (95% CI 2%–34%). The relative risk of experiencing a hip fracture in the ITT population was reduced by 15% but this did not reach statistical significance, as the study was not powered for this parameter. An analysis on a high-risk group suggested by the European regulatory authorities (women aged 74 years and over plus a femoral neck BMD less than T score of -3 SD which was equivalent to NHANES T score of -2.4 SD) showed that strontium ranelate reduced hip fracture risk by 36% (95% CI 0–59%, $p = 0.046$).⁹

In a preplanned pooled analysis of patients aged 80 and over in both the SOTI and TROPOS studies (1488 patients included), strontium ranelate reduced the risk in the first year of vertebral fracture by 59% (95% CI 25%–78%) and non-vertebral fractures by 41% (95% CI 5%–63%). At 3 years the risk reductions were 32% (95% CI 8%–50%) and 31% (95% CI 8%–48%) respectively.^{10,11}

In a follow up pooled analysis at 5 years in this age group, the relative risk reductions were maintained: 31% for vertebral fractures (95% CI 8%–48%) and 26% for non-vertebral fractures (95% CI 5%–43%).¹²

Teriparatide

The pivotal trial involving teriparatide was the Fracture Prevention Trial (FPT), which showed that after daily subcutaneous injection of 20 micrograms for a median duration of 21 months, new vertebral fractures were reduced by 65% (95% CI 45%–78%) and new non-vertebral fragility fractures were reduced by 53% (95% CI 12%–75%), compared to placebo.¹³ The full age range however was not stated in the paper. In a subsequent published post hoc analysis from the FPT, the age range of the ITT postmenopausal population studied was reported as 42–86 years.¹⁴

In this analysis subgroups were defined according to patient age younger than 75 years (841 patients) and 75 years or older (244 patients). There were no significant treatment-by-age interactions for vertebral or non-vertebral fragility fractures, indicating that the clinical effects of teriparatide were consistent in both older and younger women.¹⁴

Other licensed treatments

Calcitonin and raloxifene

There are currently no fracture outcome trials for the use of calcitonin or raloxifene in patients over the age of 80 years.

Conclusion

Only a few RCTs investigating anti-osteoporotic agents with fracture endpoints have included subjects (women) over the age of 80 years. The only bisphosphonates with significant data in this age group are risedronate and zoledronate. Risedronate showed a significant reduction in new vertebral fractures by 1 year and maintained reduction at 3 years. A post hoc analysis published as an abstract on a high-risk group (established osteoporosis, age 70–100 years) has shown a significant reduction in hip fractures. With regards to zoledronate, there was a significant reduction in all clinical fractures, vertebral and non-

vertebral fractures in both studies. New hip fractures were also significantly reduced in the PFT trial group. There was a significant 28% relative reduction in risk of death in the RFT trial group compared to placebo. Further analysis is required to look into the data of zoledronate in the over 80s subgroup.

For strontium ranelate, a pre-planned pooled analysis of published abstracts have shown new vertebral and non-vertebral fractures are significantly reduced at 1, 3 and 5 years in subjects aged 80 years and over. A subgroup analysis designed to show a reduction in non-vertebral fracture showed that in a high-risk group (age 74–100 years, NHANES T < -2.4), hip fractures were significantly reduced. For teriparatide the main RCT showing a significant reduction in vertebral and non-vertebral fractures after a median of 21 months treatment, included subjects up to the age of 86 years. A published subgroup analysis showed that the effects were consistent among the over-75 and under-75 year age group.

There is thus limited data available on the efficacy of anti-osteoporosis treatments in the over 80s with regards to fracture reduction. However, some data is available from RCTs involving risedronate, strontium ranelate, zoledronate and teriparatide for this particular age group. The evidence for efficacy in reducing fractures in patients over the age of 80 is needed for all treatments at both spine and femoral neck.

Current evidence in the over 80 year old age group only exists for strontium ranelate in the prevention of vertebral fractures—no other treatments have statistically significant published outcomes at the spine, and no treatments have evidence that support efficacy at the femoral neck. Treatments should be aimed at reducing vertebral and hip fractures in this age group with considerations given to treatment efficacy but also to medication tolerance and compliance.

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