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Invited speaker abstracts

IS2

Overview of current treatments and the potential role of combination therapies in osteoporosis

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The current therapies of osteoporosis can be divided into antiresorptive and bone forming therapies. The antiresorptive therapies comprise bisphosphonates, denosumab, SERMs, and HRT. The most efficient antiresorptive therapies reduce the risk of vertebral, non-vertebral and hip fractures by approximately 70%, 20% and 40%, respectively. The bone forming therapies are teriparatide and abaloparatide (currently only available in the US). Both stimulate the osteoblast through the PTH receptor and reduce the risk of vertebral and non-vertebral fractures by approximately 80% and 50%, respectively. Thus, efficient therapies are available for the treatment of osteoporosis, however, there are still unmet needs. Antiresorptive therapies only increase bone mineral density to a certain extent and reduce the risk of non-vertebral fractures by 20%, and the effect of bone forming therapy seems to level off over time. At least in theory, combination therapy targeting both resorption and formation could be a solution. Studies have investigated combinations of teriparatide with orally and intravenously administrated bisphosphonates and denosumab. In the PaTH trial the combination of teriparatide and alendronate did not improve BMD more than with either drug alone. In fact alendronate even appeared to impair the bone forming effect of teriparatide. A combination of teriparatide and zoledronic acid results in the best of both therapies: the increase in hip BMD seen with zoledronic acid combined with the increase in spine BMD seen with teriparatide. In contrast, the combination of denosumab and teriparatide appears to have an additive effect. None of the studies investigating combination therapy were powered to allow for conclusions regarding anti-fracture efficacy.

Conclusion: Efficient antiresorptive and bone forming therapies for osteoporosis are available and while studies investigating combination therapies have shown interesting results pertaining to BMD, the lack of evidence for anti-fracture efficacy of combination therapies makes sequential treatment the currently preferred option for the management of osteoporosis.

DISCLOSURE

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IS3

Lessons from the SCOOP Study

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The SCreening for Osteoporosis in Older women for the Prevention of fracture [SCOOP] study was a community-based screening intervention, in women aged 70 to 85 years in the UK, in which osteoporosis treatment was recommended those at high risk of hip fracture using the FRAX risk assessment tool. The study delivered an average 28% reduction in the incidence of hip fracture in the screening arm, an effect that was significantly greater in those at higher risk targeted for appropriate treatment

The SCOOP results have significant impact on future healthcare policy. A potential screening approach was recommended by NICE in 2012, when it proposed that all women aged 65 years or older and men aged 75 years or older should have a fracture risk assessment using the FRAX or QFracture tools. The SCOOP study readily demonstrates the reversibility of high risk identified by FRAX. Health economic analysis of the study indicates that the cost per prevented hip fracture is less than £8 000 and that the cost per QALY gained is less than £20 000. If the SCOOP strategy was applied across the whole population of women in this age group in the UK, then almost 8000 hip fractures could be prevented each year; this could be further enhanced by mechanisms that extended the strategy to the two-thirds of eligible women who did not participate in the screening study, as well as combining osteoporosis treatment with falls prevention in eligible individuals.

Future studies should examine how this FRAX-based approach can be made available to, or accessible by, the wider community to achieve greater reductions in the number of hip fractures in the UK and elsewhere.

IS4

Zoledronate every 18 months for 6 years in osteopenic postmenopausal women: effects on fractures and non-skeletal endpoints

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Bisphosphonates prevent fractures in patients with osteoporosis, but their efficacy in women with osteopenia is unknown. Most fractures in postmenopausal women occur in osteopenic individuals, so if phar-

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maceutical intervention is to impact significantly on total fracture numbers, therapies with efficacy in osteopenic postmenopausal women are needed.

We report a double-blind trial of 2000 osteopenic, postmenopausal women, randomly assigned to receive 4 infusions of either zoledronate 5mg, or normal saline at 18-month intervals. Each was followed for 6 years. Monthly vitamin D supplements were provided but not calcium supplementation. Women were recruited using electoral rolls. Inclusion criteria were age >65 years, hip T-score between -1.0 and -2.5. Exclusion criteria were: lumbar spine T-score <-3.0, eGFR <30 mL/minute, major systemic disease, metabolic bone disease, or regular use of bone-active drugs in the previous year. The study has 80% power to detect a decrease in osteoporotic fractures of 30%.

At baseline, age was 71 (SD 5) y, BMI 27 (5), femoral neck T-score -1.5 (0.5), and 95% were white. Non-vertebral fractures (excluding skull, face, hands and feet) occurred in 148 women in the placebo group and in 101 in the zoledronate group (ITT analysis, hazard ratio 0.66 [95%CI 0.51, 0.85], P = 0.0014, NNT = 22). Height loss, a surrogate for vertebral fracture, was 9.3 (8.7, 9.9) mm in the placebo group and 7.4 (6.9, 8.0) mm in the zoledronate group (P < 0.0001). Odds ratio for prespecified adverse events were as follows: death, 0.65 (0.40, 1.046); myocardial infarction, 0.61 (0.36, 1.02); cancer 0.67 (0.50, 0.90). Odds ratio for breast cancer was 0.58 (0.34, 0.98).

These results suggest this less intensive zoledronate regimen is effective for fracture prevention in osteopenia, and that it has beneficial effects on cancer risk and, possibly, mortality. These findings have the potential to substantially broaden the target population for pharmaceutical intervention to prevent fractures, and suggest that zoledronate should be further explored for the prevention of cancer and vascular disease.

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IS5

Update on teriparatide and the VERO clinical trial

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Clinical trials comparing the anti-fracture efficacy of osteoporosis drugs as the primary outcome are lacking. We compared the anti-fracture efficacy of teriparatide with risedronate in patients with severe osteoporosis.

In this double-blind, double-dummy trial, we enrolled postmenopausal women with at least two moderate or one severe vertebral fracture (VFx) and a bone mineral density (BMD) T-score of less than -1.50.

680 women were randomly assigned to receive 20 μg of teriparatide once daily plus oral weekly placebo, and 680 to receive 35 mg of oral risedronate once weekly plus daily injections of placebo for 24 months. The primary outcome was the incidence of new radiographic VFx. Secondary, gated outcomes included new and worsened radiographic VFx, clinical fractures, and nonvertebral fractures. A prospectively planned subgroup analyses of fracture data across subgroups predefined by the following baseline characteristics: age, number and severity of prevalent VFx, prevalent nonvertebral fractures, glucocorticoid use, prior osteoporosis drugs, recent bisphosphonate use, clinical VFx in the year before study entry, and baseline BMD was carried out.

At 24 months, new VFx occurred in 5.4% of patients in the teriparatide group, as compared with 12.0% in the risedronate group (risk ratio: 0.44; 95% confidence interval [CI]: 0.29 to 0.68; p < 0.001). Clinical fractures occurred in 4.8% of patients in the teriparatide group, compared with 9.8% in the risedronate group (hazard ratio: 0.48; 95% CI: 0.32 to 0.74; p < 0.001). Nonvertebral fragility fractures occurred in 4.0% of patients in the teriparatide group and 6.1% in the risedronate group (p = 0.10). The rate ratio of all nonvertebral fragility fractures estimated with a Poisson regression model was significant in favour of teriparatide (rate ratio 0.56; 95% CI 0.35 to 0.90; p = 0.017). More patients treated with teriparatide had at least one high value of serum calcium or uric acid. 25-OH-vitamin D serum levels were lower in the teriparatide group.

Amongst postmenopausal women with severe osteoporosis, the risk of new VFx and clinical fractures was significantly reduced in patients receiving teriparatide compared with those receiving risedronate by 56% and 52%, respectively. The anti-fracture efficacy of teriparatide compared with risedronate was consistent within the various predefined subgroups.

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DISCLOSURE:

Employee and shareholder Eli Lilly and Company

IS6

Non-invasive imaging of therapeutic responses in bone

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Human imaging techniques now permit the evaluation of bone treatment responses in great detail. Advances in 3D histology might have a role in elucidating the response of bone to treatment, especially in the rarer causes of bone pathology such as osteomalacia. With potentially curative treatments such as anti-FGF23 on the horizon for XLH and TIO, there are good reasons to consider what 3D histological imaging techniques can provide by way of unmineralised and mineralised tissue quantification. Considering emerging osteoporosis therapies, novel non-invasive imaging techniques have shown that key skeletal regions such as the hips and spine become denser, thicker and importantly, stronger within as little as 12 months. Monthly anti-sclerostin antibody therapy and daily teriparatide injections have both been demonstrated to have rapid effects both on bone turnover, with particularly beneficial effects in osteoporotic vertebrae. In this session the advances in imaging that permit non-invasive estimation of vertebral strength, thickness and compartment-specific density will be discussed.

IS7

Understanding fibrodysplasia ossificans progressiva (FOP): genetics and biological consequences

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