DMAb subjects also showed significantly greater BMD gains compared with ALN at the lumbar spine, femoral neck, and 1/3 radius (all p<0.0125). Median serum c-telopeptide levels were significantly decreased in the DMAb group compared with the ALN group (p<0.0001) at all time points. Adverse events (AEs) and serious AEs were balanced between groups. No clinical hypocalcemic AEs were reported [Kendler DL. *J Bone Min Res* 2010].

In STAND, 149 women aged 70.0 ± 7.6 years had received ALN for ≥5 years. These women were slightly older and had worse hip but not spine BMD than those who were treated with ALN for <5 years. A total of 70 women transitioned to DMAb, and 79 women remained on ALN. Transitioning to DMAb for 12 months led to further significant increases in BMD of 2.95% (lumbar spine), 1.66% (total hip), and 1.02% (femoral neck). Those who remained on ALN had smaller changes in BMD of 1.55% (lumbar spine), 0.97% (total hip), and 0.25% (femoral neck). An interaction-by-subgroup analysis showed that the greater gains in BMD in the transition-to-DMAb subgroup that was exposed to ALN for ≥5 years were consistent with overall population results. Of the women who received ALN for ≥5 years, a similar number of AEs were reported in those who transitioned to DMAb and those who continued to receive ALN (81.4% and 84.8%, respectively). The most frequently reported AEs for both groups combined were nasopharyngitis (16.1%), back pain (11.4%), nausea (7.4%), bronchitis (7.4%), pain in the extremities (7.4%), and arthralgia (7.4%). There were no cases of osteonecrosis of the jaw, delayed fracture healing, or atypical femoral fractures.

According to Dr. Bone, results from the STAND follow-up study are consistent with those from the overall STAND study—ie, that the transition to DMAb after ≥5 years of continuous ALN treatment led to further significant gains in BMD at the lumbar spine, total hip, and femoral neck—and demonstrated a similar safety profile compared with patients who continued on ALN.

Results from the First Two Years of the FREEDOM Trial Extension

Written by Rita Buckley

Fracture REduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM; NCT00089791) was a randomized, placebo-controlled, Phase 3 trial designed to test the effect of denosumab on risk of fracture in postmenopausal women during a 3-year follow-up period [Cummings SR et al. *N Engl J Med* 2009]. Henry G. Bone, MD, Michigan Bone and Mineral Center, Grosse Pointe, Michigan, USA, presented findings from the first 2 years of the FREEDOM trial extension.

Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL) that blocks its binding to RANK, inhibiting the development and activity of osteoclasts, decreasing bone resorption, and increasing bone density.

A total of 7808 women aged between 60 and 90 years with osteoporosis were enrolled at 213 study sites worldwide. Subjects were randomly assigned to receive either 60 mg of denosumab or placebo subcutaneously every 6 months for 36 months. The primary endpoint was new verterbral fractures. Secondary endpoints included nonvertebral and hip fractures.

The cumulative incidence of new radiographic vertebral fractures in the denosumab group was 2.3% versus 7.2% in the placebo group (p<0.001). The cumulative incidence of hip fractures was 0.7% in the denosumab group versus 1.3% in the placebo group (p=0.04). The relative decrease in nonvertebral fractures in the treatment group was 20% (p=0.01), with no increase in the risk of adverse events

The extension study monitored crossover and safety data for up to 10 years in 4550 subjects who completed the FREEDOM trial; 2207 crossover and 2343 long-term subjects received 60 mg of denosumab every 6 months. The placebo group data reflect up to 4 doses of denosumab (2 years; crossover). The treatment group data reflect up to 10 doses over 5 years (long-term group).

During the first 2 years of treatment, the crossover group showed significant gains of 7.9% in lumbar spine BMD and 4.1% in total hip BMD (p<0.0001). The long-term group had further significant BMD increases of 13.7% in the lumbar spine and 7.0% in the total hip over the cumulative 5-year period (p<0.0001). Serum c-telopeptide of type 1 collagen was rapidly and similarly reduced after the first (crossover) or seventh (long-term) administration of denosumab.

The crossover group had lower yearly incidences of new vertebral and nonvertebral fractures than the control group. The rate of fractures in the long-term group remained low. Adverse events (AEs) and serious AEs (SAEs) in the crossover group were similar to or lower than in the placebo and denosumab FREEDOM groups. Neither AEs nor SAEs increased over time with long-term administration of denosumab.

Infection rates in Years 4 and 5 in the denosumab group were similar to or lower than yearly rates in the FREEDOM placebo group. This was also the case for individual SAEs of infection, including pneumonia, urinary tract infection, diverticulitis, gastroenteritis, cellulitis/erysipelas, and bronchopneumonia. Two oral AEs were adjudicated to osteonecrosis of the jaw in the crossover group; both healed completely, and 1 woman continued taking denosumab. No oral AEs occurred in the long-term group, and there were no atypical fractures. These outcomes are consistent with the original FREEDOM study observations.

Results from the TOM Trial

Written by Lori Alexander

Testosterone supplementation is known to increase muscle mass and strength in healthy older men. The Clinical Meaningfulness of the Changes in Muscle Performance and Physical Function Associated with Testosterone Administration in Older Men with Mobility Limitation (TOM; NCT00240981) trial [Travison TG et al. *J Gerontol* 2011] found that testosterone administration was associated with patient-important improvements in muscle strength and stair-climbing power. The authors concluded that improvements in muscle strength and only some physical function measures should be weighed against the risk of adverse events in this population. Thomas G. Travison, PhD, Boston University School of Public Health, Boston, Massachusetts, USA, presented findings from the trial—a parallel-group, double-blind, randomized, controlled study.

Participants included community-dwelling men aged ≥65 years with a total serum testosterone level between 100–350 ng/dL or free serum testosterone less than 50 pg/mL and mobility limitation. Mobility limitation was defined as difficulty walking 2 blocks on a level surface or climbing 10 steps and a summary score between 4 and 9 on the Short Physical Performance Battery. The primary outcome was leg press strength. Secondary outcomes included chest press strength, stair climb, 40-m walk, lean body mass (LBM), physical activity, self-reported function, and fatigue. Proportions of patients who exceeded minimally important differences (MIDs) in study arms were compared.

Of 4726 men who were screened, 278 met eligibility criteria; 209 were randomized to transdermal gel that contained either placebo or 10 g of testosterone for application once daily for 6 months. Subjects were stratified by age (65 to 75 years or >75 years). Testosterone was measured 2 weeks after randomization in blood samples that were drawn 2 to 4 hours after gel application. If the average of two serum testosterone values was <500 ng/dL or >1000 ng/dL, the daily dose was increased to 15 g or decreased to 5 g, respectively. Participants who used more than 90% of the gel tubes were deemed compliant; over 90% met this criterion in both groups.

The percentage of men whose leg press strength improved more than the MID was significantly greater in the testosterone group (43%) than in the placebo group (18%, p=0.01). Among participants who were assigned to the testosterone arm, increases in total and free testosterone were associated with increased leg press strength, appendicular skeletal muscle mass, and loaded stair-climb power. Lean mass gains (p<0.0001) and fat mass losses (p<0.0001) were significantly greater in the testosterone than the placebo arm. Changes in chest-press strength were associated with changes in total (r=0.34; p=0.002) and free testosterone (r=0.36; p=0.001) and changes in LBM (r=0.42; p=0.0001) and appendicular lean soft tissue (r=0.36; p=0.001).

The changes in maximal voluntary and loaded stair-climbing power were related to changes in serum testosterone concentrations. The muscle strength gains were related to both total and free testosterone concentrations. Changes in stair-climbing power and walking speed were related to changes in leg press strength, which is an important determinant of stair-climbing power and walking speed. These correlation analyses were consistent with the following mechanistic directionality: increases in testosterone levels → gains in skeletal muscle mass → increase in muscle strength → improved physical function.

Tempering the enthusiasm that was generated by the positive primary endpoint, cardiovascular (CV) adverse events (AEs) occurred in 28 participants (23 in the testosterone; 5 in the placebo arm). These events prompted the trial's Data and Safety Monitoring Board to recommend that further enrollment and administration of study medications to all participants be suspended.

The study did not include multiple treatment arms; so, it is not known if the AEs are due to the high dose of testosterone that was used, the route of administration, the duration of therapy, or other factors. Alternative regimens, such as lower doses, shorter courses, and combination with resistance training, might deliver the benefits of improved mobility and strength without the adverse CV risk that was observed in this study. Until more data are available, testosterone therapy cannot be recommended as a treatment of impaired mobility in older men.