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.