Effects of Odanacatib in the Treatment of Osteoporosis in Postmenopausal Women Previously Treated with Alendronate

Written by Maria Vinall

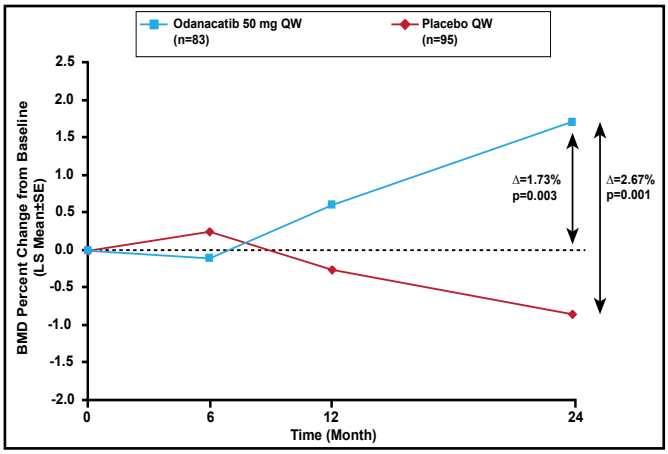
Odanacatib is a selective, potent, and reversible cathepsin K inhibitor being developed for the treatment of postmenopausal osteoporosis. Roland Chapurlat, MD, Hôpital Edouard Herriot, Lyon, France, reported results of A Study to Evaluate the Safety, Tolerability, and Efficacy of Odanacatib (MK0822) in Postmenopausal Women Previously Treated with Alendronate. The trial found odanacatib to be safe and effective for increasing bone mineral density (BMD) in postmenopausal women previously treated with alendronate.

Unlike denosumab and bisphosphonates, which reduce both bone resorption and bone formation, odanacatib inhibits bone resorption while preserving bone formation (to some extent) by limiting the digestion of the collagen bone matrix while sparing osteoclastic activity and function [Leung P et al. *Bone* 2011; Duong LT. *Bonekey Reports* 2012].

This randomized, double-blind, placebo-controlled, 24-month study evaluated the effect of odanacatib on BMD in postmenopausal patients previously treated with alendronate for ≥3 years (mean 5.5 years). Postmenopausal women aged ≥60 years (n=246; mean age 71 years and mostly white) with no previous hip fractures and BMD T-scores at any hip site between <–2.5 and >–3.5 in patients without a history of fracture (<1.5 to >–3.5 in patients with a history of fracture) received odanacatib 50 mg or placebo QW, along with vitamin D_3 5600 IU and open-label calcium supplementation to ensure a total daily intake of 1200 mg. The primary study endpoint was BMD at the femoral neck with odanacatib versus placebo at Month 24. The key secondary endpoint was BMD at the femoral neck with odanacatib compared with baseline at Month 24. Other secondary endpoints were BMD at the trochanter, total hip, lumbar spine, 1/3 radius, biochemical markers of bone resorption and formation, and safety and tolerability.

Baseline characteristics were balanced between the 2 groups. At 24 months, the percent change in femoral neck BMD was greater in odanacatib-treated patients compared with placebo (Δ=2.67%; p<0.001) and baseline (Δ=1.73%; p=0.003; Figure 1). Similar significant results for total hip, trochanter, and lumbar spine BMD were noted. There was no difference in 1/3 radius BMD between odanacatib and placebo.

Figure 1. Primary Endpoint: Femoral Neck BMD.



BMD=bone mineral density; LS=least squares; QW=once weekly..
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Odanacatib further decreased bone resorption and increased bone formation in this population of patients on long-term treatment with alendronate as suggested by the continued decreases in the urine N-telopeptide/creatinine ratio (p<0.001) and increase in serum N-terminal propeptide of type 1 collagen values (p=0.011).

Odanacatib was safe and well tolerated. The most common adverse events, which occurred at a similar rate in both groups, were back pain, arthralgia, and urinary tract and respiratory infections. The authors concluded that odanacatib may offer a viable alternative for patients who are in need of continued therapy and want to obtain benefit beyond that already provided from alendronate.

Anti-TGFβ Inhibits TGFβ-Regulated Gene Expression in Skin and Is Associated with a Rapid Decline in Skin Score

Written by Maria Vinall

In scleroderma, drug treatment of skin disease is difficult to assess due to the lack of easily measured endpoints. The modified Rodnan skin score (mRSS) is one method used to differentiate systemic sclerosis (SSc) disease subtypes, but it does not change much over short periods. Robert Lafyatis, MD, Boston University School of Medicine, Boston, Massachusetts, USA, reported results from the Fresolimumab in Systemic Sclerosis [NCT01284322] study showing that transforming growth factor-β a

(TGFβ)-response genes correlate with the mRSS and may provide a means to more quickly assess drug efficacy for skin fibrosis in early phase trials. For example, TGFβ signature genes, cartilage oligomeric protein (COMP), and thrombospondin (THS1) showed decreased expression in most SSc patients after treatment with fresolimumab (GC1008), a first-in-class pan-neutralizing anti-TGFβ human antibody.

In the first part of a Phase 2, open-label study, 7 early SSc patients were administered 2 doses of fresolimumab (1 mg/kg) at Week 0 and Week 4. Skin biopsies taken on the first day prior to treatment and at 3, 7, and 24 weeks after treatment were analyzed for gene expression by reverse transcription polymerase chain reaction, microarray, and nanostring. Seven weeks after treatment, there was a significant ($p<0.05$) decline in the primary study outcome of expression of THS1 and COMP. The relative mRNA expression of COMP and THS1 correlated with mRSS (R^2=0.44 and 0.58, respectively, for baseline skin biopsies) and with each other (R^2=0.73), suggesting these mRNAs are coregulated. Microarray data also indicate decreased expression of TGFβ signature genes, which was confirmed by nanostring data.

In general, fresolimumab was tolerated with 1 severe adverse event of severe bleeding from a patient with known gastric antral vascular ectasia. There were no malignant or premalignant lesions, or apparent aggravation of interstitial lung disease.

Skin biomarkers are sensitive measures of skin disease, offering operator-blinded assessment of mRSS. Unlike mRSS, which changes slowly, the mRNA biomarker can be assessed after a short period; thus, drug efficacy for skin fibrosis in early phase clinical trials maybe assessed more quickly.

The results of this trial showed that using skin mRNA expression biomarkers for measuring therapeutic-induced changes in SSc implicates TGFβ in SSc pathogenesis.

Inefficacy of Hydroxychoroquine in Primary Sjögren's Syndrome: Results of the JOQUER Trial

Written by Maria Vinall

The Hydroxychloroquine Versus Placebo in Primary Sjögren's Syndrome [JOQUER; NCT00632866] trial found no significant difference in the evolution of systemic disease activity, dryness, symptoms, and quality of life (QoL) in patients treated with hydroxychloroquine (HCQ) when compared with placebo. The findings were presented by Jacques-Eric Gottenberg, MD, Strasbourg, University Hospital, Strasbourg, France, in a late-breaking clinical trial.

HCQ is frequently prescribed for patients with primary Sjögren's syndrome (pSS), notably for arthralgias, synovitis, or purpura but also only for dryness and fatigue; however, except for a small crossover trial (n=19), no controlled trial has evaluated HCQ versus placebo [Gottenberg JE. ACR 2012 Abstract l9]. JOQUER was a multicenter, randomized, double-blind, placebo-controlled trial in patients with pSS. To participate, patients were required to fulfill the American-European Consensus Group criteria for the diagnosis of pSS. Patients previously treated with HCQ and those with severe systemic manifestations were not eligible for the study. Eligible participants (n=120) were randomly assigned to receive HCQ 400 mg QD or placebo, and were followed up for 24 weeks. The primary endpoint was a ≥30% improvement in the values of 2 out of 3 of the patients' visual analog scale scores evaluating dryness, pain, and fatigue between Weeks 0 and 24. Secondary endpoints were the evolution of the European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI), EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), dryness (Schirmer's test and unstimulated salivary flow), serum gammaglobulin levels, and QoL and symptom questionnaires.

Baseline characteristics were similar between the 2 groups: mean age was 56 years, median disease duration was 5 years, anti-SSA/SSB positivity was 55.1%, and median ESSDAI and ESSPRI were 2.3 and 6.2, respectively. At Week 24, 19.2% of placebo- and 19.6% of HCQ-treated patients had a favorable overall response (OR,1.07; 95% CI, 0.4 to 2.9; p=0.9; Figure 1). No significant difference was observed in the evolution of systemic disease activity, ocular or oral dryness, symptoms, and QoL. No significant difference was observed in patients with anti-SSA/SSB autoantibodies, systemic involvement, or high immunoglobulin (Ig) G levels at enrollment. A significant decrease in IgM levels (from 1.3 g/L to 1.1 g/L) with HCQ versus no difference with placebo was noted (p=0.01). Nearly all evaluated patients in the HCQ group had detectable blood levels of HCQ at 6 months. Tolerance of HCQ was comparable to placebo.

As antimalarial drugs inhibit activation of endosomal toll-like receptors and interferon (IFN) [Kuznik A et al. *J Immunol* 2011], analyses are ongoing to determine whether HCQ could have a therapeutic interest in some patients with an IFN signature.