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Idiopathic osteoporosis (IOP) in premenopausal women is a rare disease (estimated United States prevalence ~125,000) that affects young, otherwise healthy women, many of whom sustain multiple fractures or have extremely low areal bone mineral density (aBMD). There is no FDA-approved therapy for premenopausal IOP. Using transiliac biopsies and high resolution imaging, we documented heterogeneous bone remodeling (very low to frankly elevated), disrupted bone microarchitecture and markedly lower bone strength at all sites in premenopausal women with IOP. In a small open-label, pilot study of 21 women with IOP treated with 18-24 months of the osteo-anabolic drug, teriparatide (TPTD), there were marked increases in aBMD by DXA and improved trabecular microstructure and strength. In 2011, the FDA Orphan Diseases Branch funded our clinical trial, "A Phase 2 Study of Teriparatide for the Treatment of Idiopathic Osteoporosis in Premenopausal Women" (FD003902) to test the hypotheses that therapy with TPTD will safely increase areal and volumetric BMD, improve bone microarchitecture and increase bone strength. Despite slow accrual, recruitment is nearly complete, with 39 of 41 women enrolled. This renewal seeks to complete acquisition of FD003902 endpoints in all subjects (Aims 1-3), and in a new Aim 4, investigate novel predictors and mechanisms of responsiveness to TPTD. In our pilot study, 4 women (19%), who were Non-Responders to TPTD, had ~5-fold lower bone formation rate (BFR/BS) on baseline bone biopsies. They also had higher baseline serum insulin-like growth factor 1 (IGF-1), suggesting osteoblast resistance to IGF-1, a hormone that stimulates bone formation and is critical for TPTD action on osteoblasts. Our preliminary data in women with IOP show that circulating osteogenic progenitor cells (COPs), isolated by flow cytometry from peripheral blood mononuclear cells, and IGF-1 receptor (IGF-1R) density on COP cell surface increase with TPTD and that percent increase in IGF-1R density predicts increase in spine and hip aBMD with TPTD therapy. We hypothesize that response to TPTD in premenopausal women with IOP is directly related to the increase in %COP cells and IGF1-R density on COP cells, that Non-Responders will have smaller increases in both parameters than Responders, and that COP cell surface IGF1-R density before and after 3 months of TPTD will predict individual response to TPTD. We will test these hypotheses on COP cells that are being isolated prospectively during FD00390. The Specific Aims of this Renewal are to: 1. establish the efficacy and safety of 6 months of TPTD vs placebo, 2. determine the effect of 3 months of TPTD on tissue-based BFR/BS assessed by transiliac bone biopsy, and whether BFR/BS predicts TPTD response, 3. determine the extent to which 12 and 24 months of TPTD improves areal and volumetric BMD, bone microarchitecture and strength (stiffness), and 4. determine the effect of TPTD on %COP cells and IGF-1R density on COP cells, and the extent to which they predict TPTD response. Our objectives are to establish safety and efficacy of TPTD and predictors of TPTD response in premenopausal women with IOP.