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Background: Fibrodysplasia ossificans progressiva (FOP) is an ultra-rare, autosomal dominant disorder driven by mutations in ACVR1 that render it responsive to Activin A. FOP is characterized by progressive heterotopic ossification (HO) and distressing inflammatory events called "flare-ups." Flare-ups can precede new HO; however, limited prospective data exists on this phenomenon. Garetosmab (GAR), an investigational human monoclonal antibody against Activin A, blocks formation of new HO in FOP. **Methods:** This is a *post-hoc* analysis of LUMINA-1 (NCT03188666) a phase 2, randomized, double-blind, placebo-controlled study, which evaluated the safety and efficacy of GAR (10 mg/kg/week IV) versus placebo (PBO) in adult patients with FOP over 28 weeks. Patient-reported flare-ups were collected via a patient diary and severity level was reported as mild, moderate or severe. Clinician-reported flare-ups were collected as adverse events in the trial. HO lesions were imaged by ^{18}F-NaF positron emission tomography (PET) and whole-body low-dose X-ray computed tomography (CT). **Results:** There was a two-fold higher proportion of patients who reported one or more flare-ups on PBO 17/24 (71%) compared with GAR 7/20 (35%). Clinicians reported a four-fold higher proportion of patients experiencing one or more flare-ups on PBO 10/24 (42%) compared with GAR 2/20 (10%). Overall rates of flare-up events were two-fold higher on PBO vs. GAR (1.4 vs. 0.65 events/patient/28 weeks) for patient-reported events and eight-fold higher on PBO vs. GAR by clinician report (0.83 vs. 0.10 events/patient/28 weeks). Most flare-ups occurred on the extremities and back; pain was the most commonly reported symptom. Patient-reported flare-ups on PBO were more frequently reported as severe (29.4%) compared with GAR (7.7%). Among subjects with at least 12 weeks of follow-up from start of patient-reported flare-up, development of new HO near the site was 5/27 (18.5%) on PBO and (0%) on GAR. Of all new HO lesions, 41% on PBO and 0% on GAR occurred with spatial and temporal relation to flare-up. **Conclusions:** Approximately two-thirds of patients on PBO reported flare-ups over 28 weeks. GAR was associated with reductions in frequency and severity of flare-ups. Fewer than 20% of patient-reported flare-ups were associated with new HO, indicating frequent discordance of these phenomena, and compatible with previous reports. GAR's ability to reduce patient- and clinician-reported flare-ups, as well as new HO lesions may provide an important therapeutic option.

Bone and Mineral Metabolism

NOVEL TREATMENTS FOR METABOLIC BONE DISEASES

Sequential Therapy With Recombinant Human IGF-1 Followed by Risedronate Increases Spine Bone Mineral Density in Women With Anorexia Nervosa

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Anorexia nervosa is complicated by low bone mineral density (BMD) and increased fracture risk associated with low bone formation and high bone resorption. The spine, particularly its trabecular component as measured by lateral spine dual-energy x-ray absorptiometry (DXA), is most severely affected. Low BMD and bone formation are associated with relative insulin-like growth hormone-1 (IGF-1) deficiency. Our objective was to determine whether bone anabolic therapy with off-label recombinant human (rh) IGF-1 followed by antiresorptive therapy with risedronate would increase BMD more than risedronate alone or placebo in women with anorexia nervosa. We conducted a 12-month, randomized, placebo-controlled study of 90 ambulatory women with anorexia nervosa and low areal BMD (aBMD) (Z- or T-score <-1.0). Participants were randomized to 1 of 3 groups: 6 months of rhIGF-1 (starting dose 30 mcg/kg SQ BID) followed by 6 months of risedronate (35mg PO weekly) ("rhIGF-1/Risedronate") (n=33), 12 months of risedronate (35mg PO weekly) ("Risedronate") (n=33), or double placebo ("Placebo") (n=16). Participants received calcium 1200 mg and vitamin D 800 IU daily. rhIGF-1 was titrated to maintain IGF-1 levels within the age-adjusted normal range. Main outcome measures were aBMD at the spine [1° endpoint: postero-anterior (PA) spine BMD], hip, and radius by DXA, and vertebral, tibial, and radial volumetric BMD (vBMD) and estimated strength by multi-detector computed tomography (MDCT) or high-resolution

peripheral quantitative CT (HR-pQCT). At baseline, mean age [28 ± 7 y (mean ± SD)], BMI (18.5 ± 1.9 kg/m^2), and BMD were similar among groups. At 12 months, mean PA spine aBMD was higher in the rhIGF-1/Risedronate (p=0.03), and trended towards being higher in the Risedronate (p=0.08), group than the Placebo group. Mean lateral spine aBMD was higher in the rhIGF-1/Risedronate than either the Risedronate (p=0.002) or Placebo (p=0.04) groups. From baseline to 12 months, mean PA and lateral spine aBMD increased by 1.9 ± 0.6% and 4.2 ± 1.0% in the rhIGF-1/Risedronate (p<0.05), 1.7 ± 0.8% and 1.7 ± 1.0% in the Risedronate (p=NS), and decreased by 0.3 ± 0.8% and 1.1 ± 1.3% in the Placebo (p=NS), groups, respectively. Areal BMD Z-scores did not normalize in any group. At 12 months, vertebral vBMD by MDCT was higher (p<0.05), and vertebral strength trended towards being higher, in the rhIGF-1/Risedronate than Placebo group. Neither hip or radial BMD, nor radial or tibial estimated strength, by HR-pQCT differed among groups. rhIGF-1 was well tolerated. In conclusion, sequential therapy of 6 months of rhIGF-1 followed by 6 months of risedronate increased lateral spine aBMD, the site most severely affected in women with anorexia nervosa, more than risedronate or placebo. These data suggest that strategies that are anabolic and antiresorptive to bone may be most effective in increasing BMD in women with anorexia nervosa.

Bone and Mineral Metabolism

NOVEL TREATMENTS FOR METABOLIC BONE DISEASES

TransCon PTH as a Hormone Replacement Therapy for Patients with Hypoparathyroidism: 6-Month Update from the PaTH Forward Open-Label Extension

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Background: Hypoparathyroidism (HP) is characterized by insufficient levels of parathyroid hormone (PTH), resulting in hypocalcemia, hyperphosphatemia, hypercalciuria, and a reduced quality of life (QoL). PTH replacement therapy should restore physiologic levels of PTH and restore downstream physiologic levels of calcitriol, promoting independence from Ca and active vitamin D supplements and normalization of QoL.
TransCon PTH is an investigational long-acting prodrug of PTH(1–34) for the treatment of HP. During the initial 4-week fixed-dose period of the PaTH Forward Trial, TransCon PTH enabled 82% of subjects to achieve independence from standard of care (SoC; no active vitamin D and Ca ≤ 500 mg/day) compared to 15% with placebo. Here, we report 6-month (Week 26) results from the open-label extension (OLE).
Methods: PaTH Forward is a phase 2, double-blind, placebo-controlled trial evaluating TransCon PTH in adult HP patients treated with SoC. Subjects received fixed doses of TransCon PTH 15, 18, or 21 µg PTH(1–34)/day or placebo for 4 weeks, followed by an OLE period during which TransCon PTH dose was titrated (6–30 µg PTH[1–34]/day) per individual dosing requirement. Safety and efficacy endpoints were evaluated at predefined timepoints over the OLE. Endpoints were evaluated at Week 26 including 1) sCa, 2) 24-hour uCa, 3) independence from active vitamin D, and 4) independence from therapeutics doses of oral calcium. QoL was assessed by the SF-36 and the Hypoparathyroidism Patient Experience Scales (HPES).
Results: All 59 subjects completed the initial 4-week period and continued in the OLE; 58 subjects continue in the OLE beyond 6 months (1 withdrew unrelated to safety or efficacy). TransCon PTH enabled independence from SoC (no active vitamin D and Ca ≤ 500 mg/day) in 91% of subjects and independence from all supplements (no active vitamin D and no Ca) in 76% of subjects by Week 26. Mean 24-hour uCa decreased from a baseline mean of 415 mg/24h to 178 mg/24h by Week 26 (n = 44) while maintaining sCa, and reducing sP and CaxP to fall within the normal range. The mean scores for all SF-36 summary and domains increased from below normal at baseline to within the normal range by Week 26. The HPES Symptom and Impact scores continuously improved through 26 weeks for TransCon PTH and placebo subjects switching to TransCon PTH. TransCon PTH continued to be well-tolerated with no treatment-related serious or severe adverse events.
Conclusions: Results from the OLE of the PaTH Forward Trial demonstrated that TransCon PTH continued to enable independence from active vitamin D and Ca supplements for most subjects while maintaining normal sCa, sP, uCa, and demonstrating enhanced quality of life, supporting its potential as a hormone replacement therapy for patients with HP. TransCon PTH will be further evaluated in the phase 3 PaTHway Trial.

Bone and Mineral Metabolism

PARATHYROID AND RARE BONE DISORDERS

A Phase 2B, Open-Label, Dose-Ranging Study of Encaleret (CLTX-305) in Autosomal Dominant Hypocalcemia Type 1 (ADH1)

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