Alternating Parathyroid Hormone (PTH) and Alendronate Treatment Regimens Further Improve the Efficacy of Daily and Cyclic PTH Regimens in Osteoporosis Therapy

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Introduction

As the only FDA-approved anabolic agent for treating osteoporosis, intermittent PTH can only be used 18-24 months in clinical practice. However, bone mineral density rapidly decreases upon withdrawal from PTH treatment despite its potent effect of promoting new bone formation[1]. In our previous study, μCT results showed a continuous anabolic window during the first week of PTH discontinuation in ovariectomized (OVX) rats[2]. During this anabolic window, no change occurs in osteoblast and osteoclast number while bone mass and microarchitecture continue to improve.

However, after a 2-week discontinuation of PTH, osteoblast number starts to decline and osteoclast number increases significantly.To fully utilize this anabolic window, a cyclic treatment regimen with repeated cycles of on and off daily injection of PTH may be able to maximize the efficacy of PTH and extend treatment duration[3]. Furthermore, adding the anti-resorptive treatment during the off-PTH period may prevent the increased osteoclast activities and further improve the treatment. Therefore, the objective of this study is to test the effect of cyclic and sequential treatment regimens alternating PTH and alendronate (ALN, an anti-resorptive agent) on bone microarchitecture and mechanical competence.

Methods

Animals

29 female SD rats received bilateral OVX surgery at age 4 months and developed osteopenia for 4 weeks.These rats were assigned to VEH (n=6, saline for 18 weeks), PTH-VEH (n=6, PTH 40μg/kg 5x/wk for 9 weeks followed by saline for 9 weeks), cyclic PTH-VEH (n=7, PTH for 3 weeks followed by saline for 3 weeks, repeat for 3 cycles), cyclic PTH-ALN (n=5, PTH for 3 weeks followed by ALN 20mg/kg 2x/wk for 3 weeks, 3 cycles) and cyclic ALN-PTH (n=5, ALN for 3 weeks followed by PTH for 3 weeks, 3 cycles).

In vivo μCT Imaging

Sequential scans of the proximal tibiae were performed by in vivo μCT (Scanco Medical) at 10.5 μm voxel size at week-4 (OVX surgery),0, 3, 6, 9, 12, 15 and 18. The same volume of interest (VOI, Fig 1A) was identified by 3D image registration[4] in all scans and subjected to trabecular bone microstructural analysis.

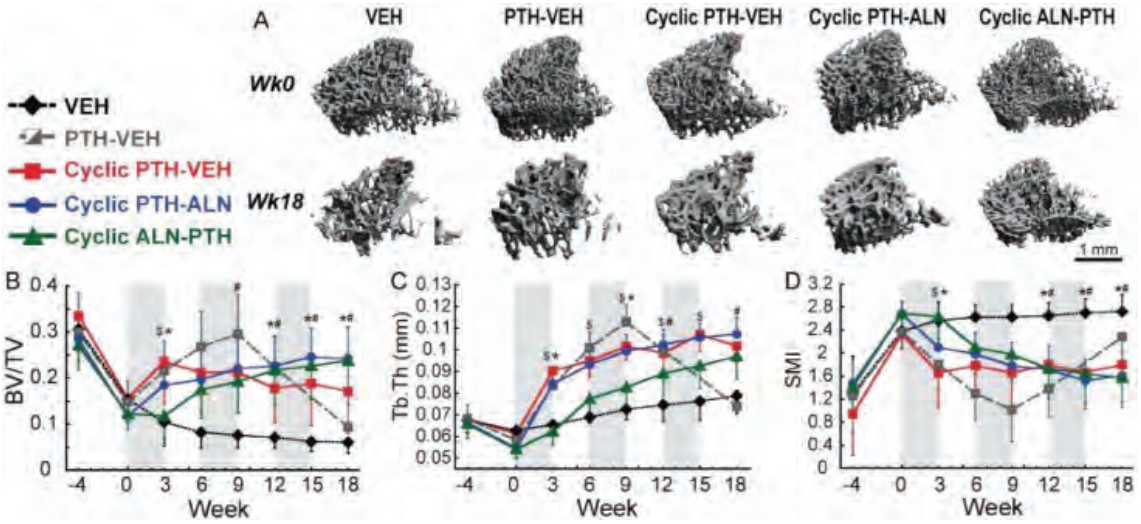

Figure 1. (A) Representative 3D images of trabecular bone microarchitecture of the proximal tibia at the baseline and end of different treatment regimes. Changes in tibial trabecular bone **(B)** BV/TV, **(C)** Tb, Th, **(D)** SMI in different treatment groups.

Ex vivo μCT Imaging

The center 2 mm of the vertebral body of lumbar vertebra L2 was imaged by μCT at 10.5 μm voxel size, and cross-sectional area (CSA) and trabecular bone microstructure were assessed. Uniaxial compression test of L2: A 4-mm-thick section of the vertebral body with processes was excised[5] and compressed to failure at a displacement rate of 1.8 mm/minute by using Instron 5542. Load-displacement curves were used to calculate peak load, stiffness, and energy to failure. Apparent-level properties, including ultimate stress, elastic modulus, and toughness, were estimated by normalizing extrinsic properties by μCT- derived total CSA, as described in[6].

Statistics

Longitudinal comparisons were made using a 2-way, repeated-measures ANOVA, adjusted for baseline values, and cross-sectional comparisons were made using 1-way ANOVA. Bonferroni corrections were applied to all post hoc tests.

Results

4-week osteopenia development in tibiae caused 51% and 11% decrease in bone volume fraction (BV/TV) and trabecular thickness (Tb.Th) respectively, and a 105% increase in structure model index (SMI, Fig 1 B-D). Bone microarchitecture deterioration continued in VEH rats for 18 weeks. Meanwhile, in PTH-VEH group, 9-week PTH treatment led to greater BV/TV, Tb.Th and lower SMI than all the other groups. However, these improvements were no longer present after the 9-week discontinuation from PTH treatment. On the other hand, cyclic PTH treatment efficiently maintained the benefit of 3-week PTH treatment in BV/TV and SMI from the 1st cycle of treatment, and further increased Tb.Th over the next 2 cycles of PTH on and off treatment. Furthermore, both alternating PTH-ALN and ALN-PTH regimens further improved the benefit of PTH treatment in BV/TV and SMI when compared to cyclic PTH-VEH regimen (Fig 1B and D). Interestingly, only the cyclic PTH-ALN regimen led to greater Tb.Th than the cyclic PTH-VEH group. Results of lumbar vertebra L2 suggested greater BV/TV and Tb.Th in both cyclic PTH-ALN and ALN-PTH groups than all the other groups (Fig 2 A-C). Additionally, peak load, energy to failure, and apparent-level toughness were 29%, 45%, and 43% greater in the cyclic PTH-ALN than the cyclic PTH-VEH group (Fig 2 D, E and H), and 29%, 48%, and 46% greater in the cyclic ALN-PTH than the cyclic PTH-VEH group, respectively. In contrast, there were no difference in any of the L2 mechanical properties among VEH, PTH-VEH, and cyclic PTH-VEH groups (Fig 2 D-I).

Discussion

Similar to previous clinical findings[1], this study showed that significant bone loss and bone microarchitecture deterioration occurred in OVX animals after discontinuation of PTH treatment. The cyclic PTH-VEH treatment regimen alleviated bone deterioration and extended the total duration of treatment. However, despite continuous increases in Tb.Th, the cyclic PTH-VEH regimen did not further improve BV/TV or SMI during the 2nd and 3rd cycles of treatment; neither did it improve any of the L2 mechanical properties by the end of the 3rd cycle. By adding antiresorptives (ALN) during the off-PTH period, both cyclic PTH-ALN and ALN-PTH regimens showed greater improvement in bone microarchitecture at the proximal tibia and lumbar vertebra when compared to cyclic PTH treatment regimen. Furthermore, cyclic treatment regimen with alternating PTH and ALN injections led to greater bone strength at both whole bone and apparent levels. In conclusion, cyclic and sequential treatment of PTH and anti-resorptive agent can further improve the treatment efficacy of daily and cyclic PTH treatment regimen and extend PTH treatment duration.

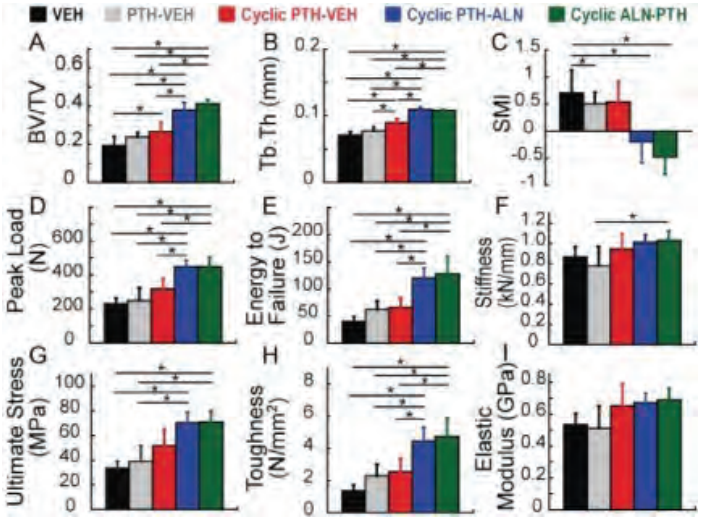

Figure 2. (A-C) Lumbar vertebra L4 trabecular bone microstructure: **(D-F)** Extrinsic mechanical properties of L4l **(G-I)** Apparent level properties, derived by normalizing extrinsic properties by total corss-sectional area * $p<0.05$

Significance

By testing various cyclic and sequential treatment regimens alternating PTH and anti-resorptive agents, this study provided important insight into the clinical design and optimization of pharmacological treatment strategies to maximize the duration and efficacy of osteoporosis treatment.

References

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