How do PINP and osteocalcin aid in monitoring FORTEO® (teriparatide injection) treatment?

SUMMARY

- The anabolic actions of teriparatide are manifested by an increase in markers of bone turnover and an increase in skeletal mass.[1-3]
- PINP is a useful marker of bone formation for monitoring patients treated with teriparatide because it increases rapidly after initiation of teriparatide, remains elevated during continued treatment, is not impacted by food or circadian rhythm effects, and has a high signal-to-noise ratio.[2,4-7]
- In several studies, early increases in bone markers, such as PINP, correlated with later increases in BMD in PMW with osteoporosis treated with teriparatide.[2,3,7-9]
- In a phase 4 exploratory, open-label, single-arm study, PMW with severe osteoporosis received teriparatide 20 µg/day; estimated lumbar spine bone strength was significantly increased from baseline to month 18 and month 24 (all p<.001). Changes in serum PINP at month 3 were correlated with the increase in estimated vertebral strength at month 18.[10]
- Osteocalcin is another marker of bone formation. Changes in osteocalcin similar to changes in PINP have been reported in studies that evaluated both markers.[5,11]
- After 2, 9, and 28 days of teriparatide treatment in an open-label, single-arm study involving osteopenic PMW, mean increases of PINP from baseline were 8.2%, >20%, and >100%, respectively. The change in osteocalcin was similar to PINP but less pronounced.[5]
- A study in PMW with osteoporosis found that changes in osteocalcin from baseline at 1, 3, and 6 months correlated with changes in spine BMD at 12 and 24 months.[12]
- An algorithm using PINP aids in monitoring response to teriparatide treatment. Patients with an absolute PINP increase of >10 µg/L are given a positive message that bone formation has increased.[4,6,8,13]
- In PMW transitioning from bisphosphonate therapy in the STRUCTURE trial, 60% and 12% of teriparatide-treated patients who had PINP increase of >10 µg/L at 1 month showed no increase (≤0%) from baseline to 12 months in total hip and lumbar spine BMD, respectively.[14]
- PINP increased rapidly with teriparatide treatment compared with placebo at 1 month in Japanese men and women with osteoporosis at high risk of fracture during a 12-month, randomized, double-blind, placebo-controlled treatment period (p<.001).[15]
- In a 12-month, randomized, double-blind, active-comparator-controlled, cross-sectional biopsy study, teriparatide significantly increased PINP in PMW with osteoporosis at months 1, 3, 6, and 12. At month 6, the levels of PINP were strongly correlated with MS/BS determined by histomorphometry at month 6.[16]
- Overall, PINP testing can support patients taking teriparatide as prescribed, which may increase the probability of clinical benefit and positive treatment outcome.[11]

INTRODUCTION – PINP AND OSTEOCALCIN

The anabolic actions of teriparatide are manifested by an increase in markers of bone turnover and an increase in skeletal mass.[1-3] During bone formation, type I procollagen is processed by the removal of procollagen type I N-terminal propeptide (PINP) and procollagen type I C-terminal propeptide (PICP) from the N- and C-terminal ends to form mature type I collagen, the most prevalent protein in bone.[11]

Markers of bone formation, PINP and PICP, make their way into the circulation where they can be assayed.[11]

PINP is a particularly useful marker of bone formation for monitoring patients treated with teriparatide because it

- increases rapidly after initiation of teriparatide
- remains elevated during continued treatment
- is not greatly impacted by food or circadian rhythm effects, and
- has a high signal-to-noise ratio.[2,4-7]

The International Osteoporosis Foundation, International Federation of Clinical Chemistry, and the National Bone Health Alliance recommend using the PINP test as the reference biochemical marker of bone formation.[11,17]

In several studies, early increases in bone markers, such as PINP, correlated with later increases in bone mineral density (BMD) in postmenopausal women (PMW) with osteoporosis treated with teriparatide.[2,3,7-9]

Finite element analysis based on quantitative computed tomography data allows researchers to estimate both vertebral strength for a simulated compression overload and femoral strength for a simulated sideways fall.[10]

In a phase 4 exploratory, open-label, single-arm study, PMW with severe osteoporosis received teriparatide 20 µg/day; estimated lumbar spine bone strength increased significantly from baseline to month 18 and month 24 (all $p<.001$).[10]

Changes in serum PINP at month 3 were correlated with the increase in estimated vertebral strength at month 18.[10]

Another marker of bone formation is osteocalcin, an abundant noncollagenous protein found in the bone matrix and produced by osteoblasts during bone formation.[11,18]

Some proportion of osteocalcin enters the circulation where it can be measured.[18] Like PINP, osteocalcin also has a high signal-to-noise ratio.[6] Changes in osteocalcin similar to changes in PINP have been reported in studies that evaluated both markers.[5,11]

In an open-label, single-arm study, serum levels of bone formation markers were measured in 15 osteopenic PMW (mean age 62 years) receiving teriparatide 20 µg/day subcutaneously for 28 days. The change in osteocalcin was similar to PINP but less pronounced (Table 1).[5]

Table 1. Increases From Baseline in PINP and Osteocalcin During Teriparatide Treatment[5]

Days	PINP	Serum Osteocalcin
2	8.2%	NA
9	>20%	>20%
28	>100%	>75%

Abbreviations: NA = not applicable, PINP = procollagen type I N-terminal propeptide.

In an open-label, single-site study in 18 healthy PMW, the immediate and short-term effects of single (40 µg) and multiple (20 µg/day for 28 days) doses of teriparatide on serum PINP and osteocalcin were measured. Teriparatide increased serum PINP and osteocalcin as shown in Table 2 and Table 3, respectively.[19]

Table 2. Immediate and Short-term Effects of Single and Multiple Doses of Teriparatide on Serum PINP[19]

Time	Teriparatide	PINP (mean ± SD)	p Value
Baseline	None	53±18 µg/L	NA
24 Hours	40 µg (single dose)	56±19 µg/L	.002
28 Days	20 µg/day	102±34 µg/L	<.001

Abbreviations: NA = not applicable, PINP = procollagen type I N-terminal propeptide.

Table 3. Immediate and Short-term Effects of Single and Multiple Doses of Teriparatide on Serum Osteocalcin[19]

Time	Teriparatide	Osteocalcin	P Value
Baseline	None	23±11 ng/mL	NA
3 days	40 µg (single dose)	26±13 ng/mL	.017
28 days	20 µg/day	40±20 ng/mL	<.001

Abbreviation: NA = not applicable.

A study measured osteocalcin levels in a control group of PMW with osteoporosis and in PMW with osteoporosis treated with teriparatide. Changes in osteocalcin from baseline at 1, 3, and 6 months correlated with changes in spine BMD at 12 and 24 months.[12]

PINP AS AN AID FOR MONITORING TERIPARATIDE TREATMENT

When monitoring teriparatide's response, PINP may be useful. A least-significant-change approach has been evaluated in several clinical trials. According to this approach, PINP is measured at baseline and after 1 to 3 months of therapy.[4,6,8,13]

Patients with an absolute PINP increase of >10 µg/L are given a positive message that

- bone formation as assessed by PINP has increased, and
- they should continue their treatment for the full prescribed course of therapy.[4,6,8,13]

Patients with a PINP increase of ≤10 µg/L should be assessed for

- their adherence
- administration
- storage techniques, and
- any conditions that might limit responsiveness to teriparatide.[4,6,8,13]

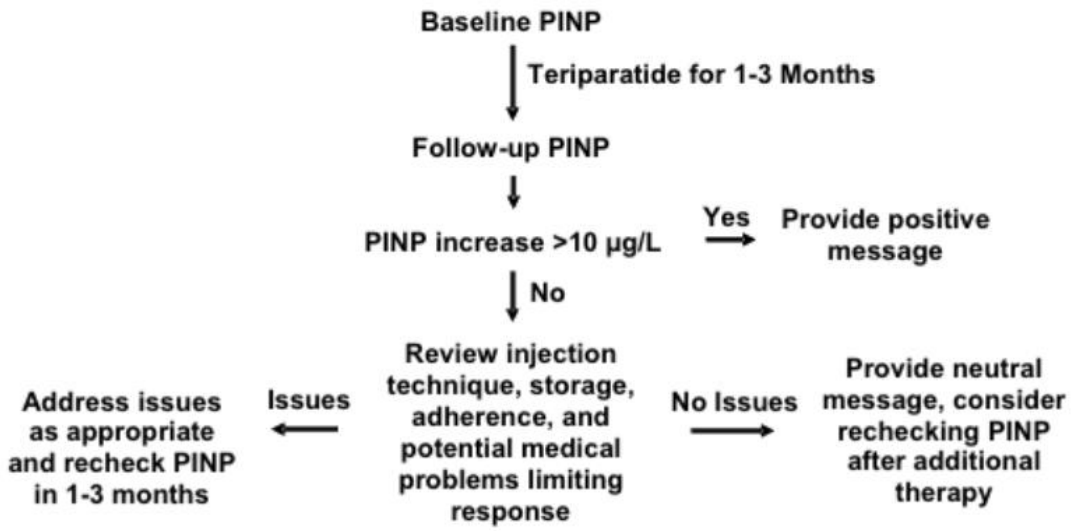
If problems are identified and corrected, PINP may be assessed after additional adherent therapy.[8]

Patients with a PINP increase of ≤10 µg/L without identifiable problems may have a repeat PINP after additional therapy since many patients with additional compliant therapy will subsequently demonstrate an increase of >10 µg/L.[8]

If a compliant patient shows no significant increase in PINP after repeat testing and no increase in BMD, consideration may be given to discontinuation of teriparatide.[8]

The algorithm for using PINP to monitor patients treated with teriparatide has been illustrated in Figure 1.

Figure 1. Algorithm for Using PINP to Monitor Patients Treated With Teriparatide[4,6,8,13]



Abbreviation: PINP = procollagen type I N-terminal propeptide.

PINP was serially assessed in patients receiving teriparatide versus placebo in a 12-month, phase 3, randomized, multicenter, double-blind trial.[8]

Bone turnover markers were collected at baseline, 1, 3, 6, and 12 months. Lumbar spine, femoral neck, and total hip BMD were measured at baseline, 3, 6, and 12 months. At 1 month, PINP increased and remained increased at each visit in the teriparatide treatment group. Increases in PINP at 1 month correlated best with increases in lumbar spine BMD at 12 months ($r=0.76$; $p<.01$).[8]

The proportions of patients with a >10 µg/L increase from baseline in PINP in the teriparatide group are shown in Table 4.[8]

Table 4. Teriparatide's PINP Increase From Baseline[8]

PINP >10 µg/L	Teriparatide (%)	Placebo (%)
1 Month	93	3
3 Months	87	0
6 Months	83	2

Abbreviation: PINP = procollagen type I N-terminal propeptide.

The proportion of patients with an increase in PINP >10 µg/L at 1 or 3 months and an increase in lumbar spine BMD ≥3% at 12 months were 92% of patients in the teriparatide group and 0% of patients in the placebo group (p<.001).[8]

Applying the algorithm, 95% of patients in the teriparatide group achieved a PINP increase >10 µg/L at 1 or 3 months.[8]

These results are supportive of the potential usefulness of PINP as an aid for monitoring patients during teriparatide therapy.[8]

Predictive Utility of PINP in Patients Previously Treated with Bisphosphonates

A post hoc analysis of the randomized, open-label, phase 3 STRUCTURE study investigated the utility of early changes in PINP in predicting BMD response in PMW with osteoporosis who switched from bisphosphonate therapy to either romosozumab (210 mg once monthly; n=218) or teriparatide (20 µg once daily; n=218) for 12 months.[14]

At month 1, 95% of romosozumab-treated patients and 91% of teriparatide-treated patients had PINP increase of >10 µg/L from baseline. Among these patients, the percentage of patients with no increase (≤0%) from baseline to month 12 in the total hip and lumbar spine BMD was

- 60% and 12%, respectively, in the teriparatide group, and
- 18% and 3%, respectively, in the romosozumab group.[14]

Among the patients with a PINP increase >10 µg/L at month 1, the percentage of patients with ≥3% increase from baseline to month 12 in the total hip and lumbar spine BMD was

- 18% and 66%, respectively, in the teriparatide group, and
- 46% and 91%, respectively, in the romosozumab group.[14]

Other Studies on PINP Response to Teriparatide

A multicenter study assessed the safety and efficacy of teriparatide 20 µg/day in Japanese men and women (N=207) with osteoporosis at high risk of fracture during a 12-month, randomized, double-blind, placebo-controlled treatment period followed by second and third treatment periods (to 18 and 24 months, respectively).[15]

Teriparatide significantly increased BMD at the lumbar spine L2 to L4 (p<.001), femoral neck (p=.015), and total hip (p<.001) compared with placebo after 12 months.[15]

PINP increased rapidly with teriparatide treatment compared with placebo at 1 month (p<.001) and then remained high through 24 months.[15]

A post hoc analysis did not find a correlation between PINP levels and calcium levels.[20]

In a 12-month, randomized, double-blind, active-comparator-controlled, cross-sectional biopsy study, healthy PMW with osteoporosis were randomized to receive

- teriparatide 20 µg once daily (n=34), or
- intravenous zoledronic acid 5 mg (n=35).[16]

The primary endpoint was mineralizing surface/bone surface (MS/BS) at 6 months post treatment. MS/BS was significantly higher in the teriparatide group than in the zoledronic acid group (median: 5.60% vs 0.16%; p<.001).[16]

Teriparatide significantly increased PINP at months 1, 3, 6, and 12.[16]

By month 1, treatment with zoledronic acid decreased the level of PINP significantly below baseline, which remained low through month 12. At month 6, the levels of PINP were strongly correlated with MS/BS.[16]

A review of clinical trials data found that the data generally supported the conclusion that an increase in PINP during teriparatide treatment is associated with increases in BMD and bone strength; still, increases in PINP during teriparatide treatment have not been directly validated to predict fracture risk reduction.[11]

Overall, PINP testing can support patients taking teriparatide as prescribed, which may increase the probability of clinical benefit and positive treatment outcome.[11]

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Enclosed Prescribing Information

FORTEO® (teriparatide injection), Lilly

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The published references below are available by contacting 1-800-LillyRx (1-800-545-5979).

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