Review Article

CLINICAL USE OF TERIPARATIDE IN THE REAL WORLD: INITIAL INSIGHTS

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ABSTRACT

Objective: To summarize expert opinion regarding clinical application of the recently introduced anabolic agent teriparatide [human parathyroid hormone (1-34)] in treatment of postmenopausal osteoporosis in women, and osteoporosis in men.

Summary: The anabolic agent teriparatide was approved for clinical use by the Food and Drug Administration (FDA) on November 26, 2002. Since the launch of teriparatide, many more questions about clinical use of this exciting agent have emerged than there are answers provided by clinical trials or FDA-approved product labeling. A group of clinicians with a broad range of experience in research and clinical applications of teriparatide met recently to address practical issues related to its use. This manuscript is a compendium of the consensus opinions of the authors that attempts to provide practical answers to many real-world questions being asked about teriparatide therapy since its approval by the FDA. **(Endocr Pract, 2004;10:139-148)**

Abbreviations:
BMD = bone mineral density; **BSAP** = bone-specific alkaline phosphatase; **DXA** = dual energy x-ray absorptiometry; **FDA** = United States Food and Drug Administration; **LSC** = least significant change; **PTH** = parathyroid hormone

INTRODUCTION

The United States Food and Drug Administration (FDA) approved the recombinant form of teriparatide [human parathyroid hormone (1-34); (Forteo, Eli Lilly and Company, Indianapolis, IN, USA)] for clinical use on November 26, 2002. Product labeling regarding use of teriparatide can be viewed in the package insert of this new therapy for osteoporosis. Indications, contraindications, and guidance for monitoring teriparatide therapy are summarized in Tables 1 through 4. These recommendations are based on data from a pivotal clinical trial and additional smaller studies in men and postmenopausal women (1-2).

As would be expected with the initial use of any therapeutic agent, questions concerning use of teriparatide have arisen since its approval. In an attempt to provide early answers to these questions, clinicians with wide-ranging experience with investigational and clinical use of teriparatide met in a workshop setting to discuss common questions and formulate advice regarding how best to use this new agent. Admittedly, the resulting recommendations more often reflect individual opinion and perspective than evidence-based conclusions.

Undoubtedly, as experience with teriparatide becomes more extensive and more data are brought to bear on the issues discussed in this paper, ideas about teriparatide therapy will change. We feel, however, that there is a pressing current need to identify and answer common questions about teriparatide, and we offer our views in the hope that they may help clinicians manage their patients better using this promising new therapeutic agent.

This report is based upon the following 6 key goals identified during our meeting:

1. Develop a framework for identifying patients who should and should not be considered for teriparatide therapy
2. Recommend a core set of baseline tests that should be considered before initiating teriparatide therapy
3. Recommend approaches to monitoring patients receiving teriparatide
4. Consider the influence of previous or concurrent antiresorptive therapy on teriparatide use
5. Consider ways in which bone density can be maintained after teriparatide is discontinued
6. Discuss "real-world" issues in teriparatide therapy, including adverse events, utilization, and reimbursement

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These questions make up the framework for the following statements, which reflect the consensus of the group.

CONSENSUS STATEMENTS

Who Should be Considered for Teriparatide Therapy?

Consistent with FDA guidelines, we agree that teriparatide treatment should be reserved for patients with osteoporosis who are at "high-risk" for fracture. Guidelines for identifying such patients are summarized in Table 1. Certainly, patients who have sustained one fragility fracture are at high risk for having another (3-5). Second, patients with T-scores below –3.0 at the lumbar spine, hip, or forearm could be at high risk, especially if they are over 70 years of age and/or have other well-defined risks for fracture.

Patients who sustain fractures while on antiresorptive regimens or are losing bone mass (i.e., exceeding the least significant change [LSC] of serial measurements) should be considered candidates for teriparatide therapy, even though these two concerns cannot be equated with treatment failure. Incidentally, clinicians performing dual x-ray absorptiometry (DXA) must know how to determine LSC values before accurate interpretations of serial BMD (bone mineral density) changes can be made (6,7). Also, while the definition of "nonresponse" to therapy may be controversial, patients who lose significant BMD should be considered non-responders or noncompliant patients.

Likewise, patients may continue to sustain fractures while on effective antiresorptive therapy. This circumstance is not necessarily due to therapeutic failure, as no existing therapeutic agent completely abolishes fracture risk (8-14). In fact, results from most clinical trials demonstrate that fracture reduction occurs in approximately 50% of cases, so a substantial percentage of all individuals on appropriate therapy will sustain further fractures (8-14). Thus, a fracture event in the presence of seemingly appropriate antiresorptive therapy does not necessarily indicate treatment failure, but does raise significant concerns. In these patients, an aggressive search for secondary causes of bone loss should be undertaken, and poor treatment compliance with the antiresorptive regimen must be considered (15). Without evidence that adding to or changing teriparatide therapy will prevent further fractures beyond the reduced risk achieved by antiresorptive therapy, teriparatide is nevertheless a reasonable option.

Teriparatide may also be indicated for patients who have had a reasonable response to therapy with antiresorptive agents (i.e., improvement in BMD with no fragility fractures) but who still have remarkably low T-scores. Low T-scores are of particular concern in patients on long-term antiresorptive therapy in whom improvements become less dramatic over time. This view recognizes an opposing one: namely that such patients may be doing about as well as can be expected, so converting to teriparatide therapy may not bring additional clinical improvements. Inertia on the part of the physician with regard to changes in course is, therefore, understandable. We nevertheless feel that in some patients with advanced age, prevalent vertebral fractures, or low BMD level, the persistent high risk of additional fractures justifies teriparatide therapy (16-19) (Table 1).

While it is recognized that fracture incidence increases as the number of risk factors for fracture increase, it is not as clear that the benefit of fracture reduction with osteoporotic therapy improves as the number of risk factors increase (20-21). Thus, from currently available data, the benefit of intervention may not be a function of baseline patient fracture risk, though these findings may be somewhat biased, as most osteoporosis-treatment clinical trials have involved higher-risk patients. Nevertheless, clinicians intuitively

Table 1
Indications for Teriparatide Administration

- High-risk patients (those with prevalent vertebral fractures, T-score of –3.0 or lower, or increased age [women and men 70 years of age or older])
- Patients losing BMD on currently available osteoporosis-specific pharmacological agents without an identifiable secondary cause
- Patients sustaining fractures without an identifiable secondary cause while on currently available osteoporosis-specific pharmacological agents
- Patients with glucocorticoid-induced osteoporosis (off-label indication)
- Patients who cannot tolerate an oral bisphosphonate or in whom administration of an oral bisphosphonate may not be safe (scleroderma esophagus, achalasia, etc)

BMD = bone mineral density.

consider additional therapies for patients perceived to be at persistently high-risk for additional fracture.

Teriparatide therapy may also be appropriate for patients who ordinarily would be candidates for oral bisphosphonate or raloxifene therapy, but for whom there are contraindications or issues of intolerance. Patients who, for example, have gastrointestinal intolerance to a bisphosphonate, or who have lower extremity venous disease or a thromboembolic event that precludes raloxifene or estrogen therapy, may be appropriate candidates for teriparatide therapy, assuming that they are at high-risk as defined above. An alternative to teriparatide therapy in these instances might be the off-label use of the intravenous bisphosphonates pamidronate or zoledronate. Use of these parenteral bisphosphonates is associated with increases in bone density and reductions in bone turnover, though data associating these surrogate markers of treatment efficacy with fracture reduction are not currently available**.**

Glucocorticoid-induced osteoporosis is a particularly noteworthy disorder for which teriparatide might be considered. Although both alendronate and risedronate are registered for treatment of glucocorticoid osteoporosis (22-24), FDA approval of teriparatide does not specifically name glucocorticoid-induced osteoporosis as an indication for therapy. The terminology "high-risk" would, however, certainly include some patients receiving glucocorticoids. Individuals who are to receive prolonged, high-dose glucocorticoid therapy, and who would therefore be at high risk would be, in our view, candidates for teriparatide therapy. This view does not necessarily include premenopausal women on glucococorticoids, in whom the risks of teriparatide therapy are unknown. Although no fracture data are available regarding postmenopausal women with glucocorticoid-induced osteoporosis treated with teriparatide, observed changes in bone density, bone markers, and recent data on changes in bone geometry suggest that teriparatide may well lead to fracture reduction in these individuals (25-27).

Is teriparatide necessarily *the* drug of choice for patients with osteoporosis at high risk for fracture? Bisphosphonates are also highly efficacious in such individuals. In fact, the major clinical trials with alendronate and risedronate and raloxifene enrolled patients at high risk for fracture. These pivotal clinical trials clearly show that antiresorptive agents reduce incident vertebral fracture in high risk patients (7-13). Bisphosphonates also reduce the incidence of nonvertebral fractures, including hip fracture. In patients with recent vertebral fracture, in whom the risk for a subsequent vertebral or hip fracture is high if left untreated, risedronate has been shown in prospective trials to reduce vertebral fracture risk within one year of therapy (28). In post-hoc analyses, alendronate and raloxifene also reduced clinical vertebral fractures (29-30). Thus, there is evidence of rapid reduction in fracture events with use of the antiresorptive agents. In the case of teriparatide, the study design (x-rays prior to treatment and 18 months after treatment was started) does not allow one to draw similar conclusions about a "rapid" therapeutic effect of this agent (1). In fact, the time course of non-vertebral fracture events suggests that teriparatide may not significantly reduce fractures until after approximately 1 year of therapy. On the other hand, preclinical data support rapid effects of teriparatide on bone geometry, bone microarchitecture, and increased bone strength, even though the remodeling space increases with early teriparatide use (31-37). Impressive effects of teriparatide on the elements of bone strength such as trabecular connectivity and cortical width (38-39) may be expected to promote early fracture reduction as well, especially at the lumbar spine.

One can quite reasonably wonder about the rationale for using teriparatide, which is much more expensive than the bisphosphonates, in treatment of patients at high risk for oteoporotic fracture, in whom both teriparatide and the bisphosphonates may lead to fracture risk reduction of similar magnitude, as appears to be the case based on existing data. While bisphoshonates maintain microarchitecture that may contribute to improvements in bone strength (40-42), we note that additional parameters of bone quality are affected by teriparatide (39). If one has the option to use a therapeutic agent that may restore or reconstruct skeletal microstructure and favorably influence geometrical parameters of bone therefore, it is attractive to use it.

Who Should Not be Considered for Teriparatide Therapy?

Certainly, individuals who do not have advanced osteoporosis at high risk for fracture should not be considered for teriparatide therapy. This agent is not recommended for preventive therapy, or in patients whose T-scores or other assessments do not reflect advanced osteoporotoc disease. Patients with known contraindication to teriparatide use should, of course, not receive this drug (Table 2). A potentially unclear contraindication to its use is "prior skeletal irradiation." This FDA term is specific for therapeutic irradiation, not diagnostic irradiation. Teriparatide is, further, not to be considered for prevention of early postmenopausal bone loss, a group of patients who may have small reductions in BMD and are at low absolute fracture risk. Finally, cost considerations are important. If insurance coverage is not available and the patient cannot afford the expense of this agent, one should advise another therapeutic approach.

What Baseline Tests Should be Obtained Prior to Starting Teriparatide?

Clinical tests that we recommend prior to initiating therapy with teriparatide are listed in Table 3. We strongly advise that patients undergo serum calcium determination prior to starting teriparatide tehrapy, primarily because it is contraindicated in patients with hypercalcemia. Baseline renal function tests and creatinine clearance determinations are also useful. A routine 24-hour urine calcium determination does not appear necessary, as urinary calcium excretion did not change significantly during the pivotal clinical trial (1). In patients with history of nephrolithiasis, however, 24-urinary calcium determination should be made,

possibly in concert with other tests, to explore the etiology of the kidney stones.

Because serum uric acid levels rise slightly during teriparatide tratement, a baseline uric acid level would be helpful, particularly in patients with histories of hyperuricemia or gout. Baseline bone density should obviously be obtained, even in patients with overt skeletal features of osteoporosis or who have sustained fragility fractures. Our group also felt that since teriparatide has a major effect on markers of bone turnover, baseline evaluation of these markers might be useful. Patients should therefore undergo baseline evaluation of the bone formation marker bone-specific alkaline phosphatase (BSAP) or osteocalcin, and a bone resorption marker [collagen-cross links: N- or C-telopeptide (NTX or CTX) or pyridinoline (DPD)] (43-44). The total alkaline phosphatase level could be ordered first, since it is less expensive than the BSAP, and if this value is elevated, the BSAP can be ordered to identify the tissue source of the total alkaline phosphatase. Since teriparatide is contraindicated in patients with unexplained elevations of BSAP, an alkaline phosphatase level should be determined at baseline both for initial assessment purposes and for possible monitoring over time. If the BSAP level is elevated, a search for the etiology of the increased BSAP is indicated (Paget's disease, metastatic disease to bone, hyperparathyroidism, osteomalacia, etc), as teriparatide would be contraindicated in such cases.

We also recommend that baseline 25 hydroxyvitamin D (25 OHD) and parathyroid hormone (PTH) levels be obtained before initiating teriparatide therapy. Vitamin D insufficiency is relatively common, and can be associated with elevated PTH levels. The normal range for 25-OHD, the storage form of vitamin D, should be above the now accepted lower limit of the normal physiological range (20 ng/ml), not the laboratory reference range (9 ng/ml) (45). The need for measuring PTH before starting therapy is in part because PTH elevation could reflect an occult vitamin D deficiency. Another reason is that a new phenotype of primary hyperparathyroidism is now recognized, in which serum calcium levels are normal but PTH levels are elevated. These patients do not have any obvious cause for secondary hyperparathyrodism, and in fact, may represent the earliest manifestation of primary hyperparathyroidism (46). It would seem unwise to begin teriparatide therapy in patients with even the earliest manifestations of primary hyperparathyroidism. Our group felt that a PTH level above the normal range in a normocalcemic patient with no other identifiable cause of secondary hyperparathyroidism contraindicates use of teriparatide. Clinical tests that we recommend prior to initiating therapy with teriparatide are listed in Table 3.

How Should Patients be Monitored While on Teriparatide?

Essential monitoring tests for patients treated with teriparatide are described in Table 4. Patients experience impressive early increases in vertebral BMD while on teriparatide therapy, according to evaluation by dual energy x-ray absorptiometry (DXA) technology (1). Increases in BMD associated with use of antiresorptive therapies are linked to fracture reduction, although the relationship between the magnitude of increase in BMD and the magnitude of fracture reduction is not proportional (47-50) Yet, serial BMD determinations are helpful in monitoring teriparatide

Table 2
Contraindications to the Use of Teriparatide*

- Hypercalcemia
- Paget's disease
- Unexplained elevation of BSAP
- Osteogenic sarcoma
- Unfused epiphysis
- Previous irradiation to the skeleton
- Pregancy or breast-feeding
- Bone cancer or metastatic cancer to bone
- Allergic reaction to PTH or to ingredients in the vehicle

*Per teriparatide prescribing information.
BMD = bone mineral density; **BSAP** = bone-specific alkaline phosphatase; **PTH** = parathyroid hormone.

Table 3
Suggested Clinical Tests Prior to Initiating Teriparatide Therapy

- BMD by DXA (spine and hip)
- Total serum calcium
- Total serum alkaline phosphatase
- 25-hydroxyvitamin D
- Parathyroid hormone
- Creatinine clearance

BMD = bone mineral density; **DXA** = dual energy x-ray absorptiometry.

therapy, and patient awareness of improvements in BMD may improve compliance (51).

In accordance with the Bone Mass Measurement Act, a regulation that applies only to the Medicare population, bone mass measurement may be permitted 1 year after initiation of an FDA-approved therapy. With teriparatide, changes in bone density in the lumbar spine are so rapid and of such a large magnitude that it is likely significant changes exceeding the LSC will be seen after 1 year of therapy. As to whether guidelines for use of BMD for monitoring results of antiresorptive agents (i.e., monitoring every 23 months after the first year of therapy) will be applicable to teriparatide is not clear. Clinicians will be influenced by these guidelines dictating reimbursement for the test, but will also recognize that there are situations in which one is justified in obtaining a bone mass measurement earlier than this relatively long 23-month waiting period.

Expected large changes in BMD apply primarily to the lumbar spine after teriparatide therapy. The hip typically shows more sluggish, less dramatic change in BMD, as is seen during therapy with antiresorptive agents as well. The distal third of the radius does not demonstrate significant increases in BMD after teriparatide therapy as measured by DXA though bone strength does appear to improve in the forearm, as the cross sectional area of the radius increases during teriparatide therapy (39). It is well known that areal changes in bone without any changes, or even a decline, in areal BMD can be associated with improvements in bone strength. On a biomechanical basis, therefore, even without any change in areal BMD, teriparatide appears efficacious at the forearm. Measurement of true bone density, as assessed by instruments such as quantitative computed tomography that measure bone mass in g/cm^3, may more completely assess the global effects of teriparatide on bone mass (52-53).

Teriparatide affects markers of bone turnover in ways opposite to changes seen after antiresorptive therapy. While antiresorptive agents reduce levels of bone turnover markers (54-57), teriparatide increases them (58). Another difference is that significant changes in levels of bone turnover markers are associated treatment with teriparatide (e.g., up to 3 times higher than baseline measurements) in contrast to the antiresorptive agents. It would appear then that bone formation markers may be useful indicators of the efficacy of teriparatide treatment. This expectation contrasts with those in the case of antiresorptive agents, in which reductions in bone turnover, although substantial, are often not great enough in individual patients to meet the criteria of significance (i.e., the LSC).

While reductions in bone resorption and bone formation marker levels are correlated with reductions in both new vertebral and non-vertebral fracture risk during treatment with the two FDA-approved bisphosphonates, the relationship between the increase in formation markers and reduction in fracture risk has not been studied regarding teriparatide therapy. It is reasonable, nevertheless, to expect that such a relationship exists. The increase in BSAP or osteocalcin seen as early as 1 to 3 months after initiation of teriparatide therapy has the potential to provide useful, early feedback about the effectiveness of teriparatide in a given patient.

Another point of interest regarding bone resorption markers during teriparatide therapy is that the increase in these markers does not appear to be sustained. After 12 to 18 months of teriparatide treatment, rates of bone formation and levels of bone resorption markers tend to decline to or toward baseline measurements, though more data is needed ragarding the kinetic processes involved in these changes. The eventual fall in bone marker levels with continued use of teriparatide may signal a waning of the anabolic ef-

fect on bone density, though in some clinical trials BMD continued to increase (59). This eventual decline in bone marker levels may not, therefore, signal the termination of other salutary effects of the drug on other bone qualities. Certainly, available fracture data suggest that teriparatide has effects that extend well beyond dynamic changes in bone markers (60).

What safety endpoints are reasonable to monitor with regard to teriparatide? Existing clinical trials with teriparatide indicate no major risk of hypercalcemia at the FDA-approved dosage of 20 μg daily. Nevertheless, we feel that it is prudent to obtain a serum calcium level 1 month after starting teriparatide therapy, with blood samples obtained within 16 hours after the last dose of teriparatide. Other monitoring parameters are optional, as there is no evidence that patients develop hypercalciuria or abnormalities in liver or renal function. In patients with elevated serum uric acid levels or in whom these levels are in the upper range of normal, it seems useful to remeasure serum uric acid levels within a month of initiating teriparatide therapy.

Should Antiresorptive Agents be Continued or Stopped When Teriparatide Therapy is Begun?

Many patients who may be candidates for teriparatide are currently on antiresorptive agents. In patients previously treated with estrogen, teriparatide appears to be associated with prompt, significant increases in bone density (61). This observation has also been noted in patients with glucocorticoid-induced osteoporosis who have previously been treated with estrogen (27,62). In an observational study by Ettinger et al, among patients treated with a 28-month course of raloxifene (another modest antiresorptive agent), subsequent effects of teriparatide do not appear slowed (63). In the same study, patients previously treated with alendronate for 28 months were monitored after being switched to teriparatide treatment. Among these patients, bone density did not change appreciably at the lumbar spine during the first six months of teriparatide treatment, though a slight decline in bone density was noted at the hip during this period. Over the following 12-month period, however, at both the lumbar spine and hip, bone density rose at a rate comparable to that observed in previous raloxifene users (63). At the end of the 18-month observation period, however, gains in bone density among the previous alendronate users were substantially lower than those noted among previous raloxifene users. These observations raise the possibility that the use of a potent antiresorptive agent like alendronate may be associated with a sluggish initial response to teriparatide with respect to BMD. No data exist regarding this question in individuals previously treated with risedronate.

These observations led to the differing opinions that either teriparatide should not be used in patients previously treated with alendronate for any substantial period of time, or that the bisphosphonate agent should be discontinued and teriparatide treatment "held" for a 6- to 12- month period to allow bone turnover to increase. The latter view holds that the greater the inhibition of bone resorption, the longer it will take for teriparatide to improve bone density. However, other factors must be considered as well, such as the duration of suppressive action of the bisphosphonate on bone turnover. There are, however, no current data available regarding the influence of previous bisphosphonate use on other parameters of teriparatide efficacy such as bone geometry, bone microarchitecture, and fracture rate.

How should the clinician regard this vexing issue? Since there is no evidence that previous estrogen or raloxifene therapy impairs subsequent effects of teriparatide, one could continue these agents when beginning therapy with teriparatide. With alendronate, however, one may want to discontinue therapy when teriparatide is initiated, as alendronate's effects are so long lasting that there does not appear to be any rationale for waiting a period of time before beginning teriparatide. No comparable data are available for risedronate with regard to this question. One might speculate, however, that previous risedronate use may not impair subsequent effects of teriparatide on BMD to the same extent as alendronate because risedronate does not reduce bone turnover to the extent alendronate does. Risedronate may, further, be released from the bone surface

Table 4
Monitoring of Patients on Teriparatide Therapy

- Spine and total hip BMD by DXA 12 months after initiation of treatment
- Avoid forearm BMD measurement by DXA (see text)
- Possibly quantitative computerized tomography of the wrist (developmental)
- Biochemical markers of bone formation at baseline and 3-6 months after beginning teriparatide, such as bone-specific alkaline phosphatase or serum osteocalcin

BMD = bone mineral density; **DXA** = dual energy x-ray absorptiometry.

after discontinuation more quickly in the case of alendronate (64,65).

Combining Antiresorptive and Anabolic Therapy

The recent PaTH study provides interesting information regarding the question of combining antiresorptive and anabolic therapy (66). This study tested PTH (1-84) alone and in combination with alendronate compared to alendronate alone in 238 postmenopausal women with osteoporosis. Patients had not previously been treated with antiresorptive therapy. Using quantitative computed tomography, these investigators demonstrated no advantage to combination therapy compared to PTH alone. DXA analysis revealed greater increases in total hip BMD with combination therapy in this investigation, and a greater increase in total body BMD was noted with combination therapy in a related study by Finkelstein et al (67). In some respects and at some sites, the presence of alendronate seemed to retard the effects of PTH. Again, these studies provide no data regarding the effect of these agents on fracture rates or bone microarchitecture. At this point, therefore, there may not be any advantage gained by combination therapy with PTH and alendronate, though available data are very preliminary.

How Can Teriparatide's Effects on BMD be Sustained After Teriparatide Discontinuation?

The use of a relatively short-term anabolic therapy (18-24 months) raises the obvious question of what to do after teriparatide treatment is discontinued. Studies involving estrogen treatment have shown that bone mass is maintained when estrogen therapy is continued after teriparatide therapy has been stopped (62,68). Yet, these studies by Lindsay, Cosman, and Lane did not include an experimental arm in which antiresorptive therapy was discontinued, so do not evaluate what happens to BMD after discontinuation of teriparatide in the absence of ongoing antiresorptive therapy. Data from large existing clinical trials in women and men suggest that bone loss begins rapidly among patients not immediately placed on antiresorptive therapy after teriparatide discontinuation (2,68). In contrast, preliminary data from these trials suggest that BMD is maintained in patients begun on antiresorptive therapy immediately after teriparatide is discontinued. Finally, in the phase II clinical trial evaluating the effect of rhPTH (1-84) in postmenopausal women over 12 months, additional improvement was noted in spine BMD as measured by DXA when alendronate was added after PTH was discontinued (69,70).

Generalizability of conclusions reached in the above studies is limited case, however, because of lack of prospective study design and, in some instances, small patient populations. There are, further, no data available regarding microarchitectural or geometric changes after teriparatide is discontinued with or without sustained antiresorptive treatment. In an analysis of fracture incidence after teriparatide discontinuation, data from the pivotal clinical trial does not allow determination of whether bisphosphonate use was important after teriparatide therapy with regard to the prolonged fracture protection experienced by these patients, though the number of observed fracture events was small (60). Again, the post-hoc observational nature of these requires confirmation in future studies using a more rigorous experimental design. Until better evidence is available, it seems wise take measures to prevent a decline in BMD after teriparatide therapy is terminated. An antiresorptive agent, in our opinion, should therefore be used regularly after teriparatide is discontinued.

"Real-World" Issues in Teriparatide Treatment: Adverse Events, Utilization and Reimbursement

In our experience, teriparatide is well tolerated. Patients quickly learn to self-administer teriparatide by subcutaneous injection. The "pen" injector with disposable 31-gauge needles offers almost painless injection, and a nurse-educator or other knowledgeable health care professional optimizes the patient education process. A few patients have developed hypercalcemia 2 weeks after teriparatide treatment was begun. Teriparatide was discontinued in these instances, and serum calcium levels returned to normal in 2 days each case. When oral calcium intake was subsequently reduced by 500 mg/day, hypercalcemia did not recur once teriparatide therapy was restarted in these patients. In most cases, patients' original calcium intake could be resumed without hypercalcemia appearing again. Allergic wheals have been observed at the teriparatide injection site on occasion. In one case, a patient who developed severe large wheals at the injection site was successfully "desensitized" to teriparatide under treatment by an allergist. Severe headache has led to discontinuation of teriparatide therapy in one patient; in another, severe headaches were avoided when the patient drank 12 ounces of water at the time of teriparatide administration. Two patients have sustained transient heart palpitations, and one patient had to discontinue teriparatide treatment because of reproducible severe vertigo that came on 8 hours after teriparatide administration. Two patients suffered incapacitating leg cramps relieved by drinking a sports rehydration drink soon after teriparatide administration. These adverse events are rare relative to the number of patients we have collectively treated with teriparatide over the past 6 months. It is our opinion, therefore, that the vast majority of patients tolerate teriparatide without significant adverse effects.

The FDA approved the recombinant form of teriparatide with a "black box warning" because rat toxicity studies revealed the development of osteosarcoma when high doses of teriparatide were administered for prolonged periods of time. It is important for the physician to discuss results of these preclinical studies with patients and to point out that comparable tumors have not been noted among monkeys given teriparatide in a comparable manner. It is also noteworthy that in disorders of chronic PTH excess (primary and secondary hyperparathyroidism, and parathyroid carcinoma), the number of reports of osteosarcoma is extremely small (71), with the occasional report well below the incidence rate one might expect based on coincidence.

Prior skeletal irradiation is a known contraindication to teriparatide use. The teriparatide FDA label states that the drug should not be taken "if you have had radiation therapy involving your bones." The intention of the FDA in this instance was to exclude therapeutic radiation, not diagnostic skeletal irradiation, radioiodine treatment, electron beam radiation, or some forms of brachytherapy such as installation of radioactive pellets or rods into body cavities. In the latter cases the radiation therapy physician should be asked whether the patient receiving brachytherapy sustained a radiation dose sufficient to expose adjacent bone.

Concluding Comments

The introduction of teriparatide marks an exciting new advance in our field, as a safe, effective anabolic agent that improves bone density, bone microarchitecture, and bone size is now available. Patients at high risk will clearly benefit from treatment with this new agent. In this article we have discussed a number of important issues that have emerged with the approval of teriparatide. As we gain more experience with teriparatide and as more information becomes available regarding how to use it, we should be able to address many of these questions more thoroughly in the near future. Other questions still remain to be raised and await greater understanding. A representative sample of some outstanding questions related to use of teriparatide is listed below.

- Does teriparatide reduce fracture rates to a greater degree than is currently achieved by antiresorptive regimens alone?
- Can patients achieve equal clinical benefits with shorter duration or intermittent administration of teriparatide therapy?
- Can patients achieve greater clinical benefits with longer duration of teriparatide use?
- Could patients benefit by retreatment after a first course of teriparatide (i.e., a "cyclical" teriparatide regimen)?
- The past, present, and future use of antiresorptive therapy needs further clarification in the context of teriparatide use.
- Does teriparatide reduce the incidence of hip fracture?
- Does teriparatide enhance fracture healing?
- How can one practically measure the efficacy of teriparatide with indices beyond the use of bone density and bone markers?
- In addition to glucocortiocoid-induced osteoporosis, what other secondary causes of osteoporosis could conceivably be treated with teriparatide?

Although there remains much to be learned about this anabolic agent, it is clear that its availability offers clinicians new avenues of opportunity in the treatment of women and men with osteoporosis.

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