Effectiveness of Teriparatide Therapy for Prevention of Fractures in Glucocorticoid-Induced Osteoporosis

Tristan T. Stiles

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Abstract

Background: Glucocorticoids have a wide-range of beneficial effects for treating inflammatory, allergic, and immunologic conditions. However, glucocorticoid therapy can lead to increased bone resorption and reduced bone formation by inhibiting osteoblast proliferation. This bone deterioration leads to osteoporosis. When considering therapy for prevention of fractures in glucocorticoid-induced osteoporosis (GIO), teriparatide (recombinant human parathyroid hormone 1-34) is an anabolic agent that can be used to improve bone mineral density (BMD) and prevent fractures. Due to bone deterioration caused by glucocorticoid therapy, prevention of bone fractures has significant importance. While there are several choices for therapy for prevention of GIO, the anabolic agent teriparatide could show a more significant improvement of BMD and of preventing fractures resulting from GIO. The purpose of this systematic review of the literature is to evaluate the efficacy of teriparatide in prevention of fractures that can result from glucocorticoid therapy.

Methods: An extensive literature search was conducted using Medline-OVID, CINAHL, Evidence Based Medicine Reviews Multifile, and Web of Science using the search terms: teriparatide, osteoporosis, fractures, and glucocorticoids. The reference sections of each of these articles were further searched for additional relevant sources. Articles were screened and evaluated for relevance using GRADE.

Results: Two studies met inclusion criteria for this systematic review that included two randomized control trials. These studies demonstrated that patients who were on teriparatide had increased BMD. Both studies also measured fracture rates and showed a decrease favoring teriparatide.

Conclusion: There is sufficient evidence to recommend teriparatide as a therapeutic option for reversing the effects of glucocorticoid-induced osteoporosis by improving bone mineral density and preventing the occurrence of fractures, although there may still remain a question of safety that would warrant continued research.

Keywords: teriparatide, fractures, osteoporosis, and glucocorticoids.
Third Advisor
Mark Pedemonte, MD

Keywords
Teriparatide, Fractures, Osteoporosis, Therapy

Subject Categories
Medicine and Health Sciences

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Effectiveness of Teriparatide Therapy for Prevention of Fractures in Glucocorticoid-Induced Osteoporosis

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Biography

Tristan Stiles is a native Nevadan who received his Bachelor of Science degree from the University of Nevada in 2005 with a major in Biochemistry. During his undergraduate work, he spent time working as an Emergency Medical Assistant and performed research studying smooth muscle contraction in the asthmatic airway. He went on to attend Barry University in Miami, FL, where he earned his Master’s degree in Biomedical Sciences. Afterwards, he spent 3 years back in the Reno, NV area working for a large pharmaceutical research company and spent time traveling abroad before attending Pacific University’s Physician Assistant program. He is expecting to spend his first few years out of school working in primary care or emergency medicine, possibly in a rural area. His career interests in medicine include emergency medicine, family medicine, sports medicine, orthopedics, general surgery, and international health care work.
Abstract

**Background:** Glucocorticoids have a wide-range of beneficial effects for treating inflammatory, allergic, and immunologic conditions. However, glucocorticoid therapy can lead to increased bone resorption and reduced bone formation by inhibiting osteoblast proliferation. This bone deterioration leads to osteoporosis. When considering therapy for prevention of fractures in glucocorticoid-induced osteoporosis (GIO), teriparatide (recombinant human parathyroid hormone 1-34) is an anabolic agent that can be used to improve bone mineral density (BMD) and prevent fractures. Due to bone deterioration caused by glucocorticoid therapy, prevention of bone fractures has significant importance. While there are several choices for therapy for prevention of GIO, the anabolic agent teriparatide could show a more significant improvement of BMD and of preventing fractures resulting from GIO. The purpose of this systematic review of the literature is to evaluate the efficacy of teriparatide in prevention of fractures that can result from glucocorticoid therapy.

**Methods:** An extensive literature search was conducted using Medline-OVID, CINAHL, Evidence Based Medicine Reviews Multifile, and Web of Science using the search terms: teriparatide, osteoporosis, fractures, and glucocorticoids. The reference sections of each of these articles were further searched for additional relevant sources. Articles were screened and evaluated for relevance using GRADE.

**Results:** Two studies met inclusion criteria for this systematic review that included two randomized control trials. These studies demonstrated that patients who were on teriparatide had increased BMD. Both studies also measured fracture rates and showed a decrease favoring teriparatide.

**Conclusion:** There is sufficient evidence to recommend teriparatide as a therapeutic option for reversing the effects of glucocorticoid-induced osteoporosis by improving bone mineral density and preventing the occurrence of fractures, although there may still remain a question of safety that would warrant continued research.

**Keywords:** teriparatide, fractures, osteoporosis, and glucocorticoids.
To my parents and extended family members, I can’t thank you enough for your support and encouragement over the years. Though my path can never be what I intend for it, the way it has evolved has opened me to discovery beyond what I could imagine. To those classmates who have been closest and most supportive, thanks for your advice and willingness to share in this educational adventure. The wonderful faculty at Pacific University’s PA program has been invaluable, as you have dedicated yourselves to us reaching our highest educational potential and have cared about our personal well-being throughout the process.
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Figure 1: Pathophysiology of Glucocorticoid-Induced Osteoporosis Leading to Fractures

List of Abbreviations

GIO          Glucocorticoid-Induced Osteoporosis
PTH          Parathyroid Hormone
BMD          Bone Mineral Density
hPTH 1-34    Human Parathyroid Hormone 1-34
QCT          Quantitative Computed Tomography
DXA          Dual energy X-ray Absorptiometry
GC           Glucocorticoids
Effectiveness of Teriparatide Therapy for Prevention of Fractures in Glucocorticoid-Induced Osteoporosis

BACKGROUND

Glucocorticoids (GC) have a wide-range of beneficial effects for treating chronic inflammatory conditions such as asthma, rheumatoid arthritis, and systemic lupus erythematosus. They are also used for allergic, immunologic, and malignant conditions. While their benefits are extensive, chronic GC use can lead to increased bone resorption by inhibiting osteoblast proliferation causing reduced bone formation, as well as lowering intestinal calcium absorption, and renal calcium excretion. This bone deterioration leads to osteoporosis. Because of this side effect, patients on glucocorticoid therapy have increased risk of fractures (See Figure 1). Glucocorticoid-induced osteoporosis (GIO) can be rapid and is most pronounced within the first three months of use, which is followed by slower, steady bone loss with ongoing use. Patients on glucocorticoids can have changes in their bone mineral density (BMD) increasing their risk of fracture. The most common areas of fractures and those which occur the earliest, are the lumbar vertebrae. Other fracture areas caused by GIO include the hips and femoral neck. The World Health Organization defines a diagnosis of osteoporosis when BMD is 2.5 or more standard deviations below normal peak bone mass (a T-Score of -2.5 or less being osteoporotic, and a T-Score of -1 or greater being normal). Prevention of GIO and fractures that result from the condition, is aimed at reversing the effects of the glucocorticoids, either by decreasing the dose of exogenous glucocorticoid, using supplements of vitamin D and calcium, by weight-bearing exercise, or by pharmacologic
intervention to minimize or reverse bone loss. Pharmacologic therapy includes calcitonin, oral bisphosphonates, IV bisphosphonates, estrogen, selective estrogen-receptor modulators, and anabolic skeletal agents. Antiresorptive therapies, which are the bisphosphonates including alendronate and risendronate, are labeled as the first line uses (along with calcium and vitamin D supplements) for treating GIO. However, the bisphosphonates only maintain BMD. It has been suggested that combination glucocorticoid therapy in osteoporotic patients with long term treatment of antiresorptive medications, may have an increased risk of atypical supratrochanteric and diaphyseal fractures.

Teriparatide [recombinant human PTH 1-34 (Forteo, Eli Lilly and Co., Indianapolis, IN)] is an anabolic agent approved for use in the United States that can be used to improve BMD and prevent fractures. It is a bone anabolic agent used for the treatment of osteoporosis in men and women with high risk of fractures. Teriparatide may be a more rational treatment for GIO because of its ability to increase osteoblast function, decrease osteoblast and osteocyte apoptosis, and increases the differentiation of bone lining cells and preosteoblasts into osteoblasts, which improves the microarchitecture of bone and increases its strength. A meta-analysis of randomized control trials by Han et al determined teriparatide to substantially reduce the risk of fragility fracture in postmenopausal women with a 70% reduction in vertebral fracture and a 38% reduction in non-vertebral fracture. An observational study conducted over a 36 month period found that post-menopausal women with GIO who were put on teriparatide therapy for 18 months and followed an additional 18 months once teriparatide was discontinued, had an immediate reduction of clinical fractures during treatment and continued to see a
reduced incidence of fracture once treatment was stopped. Another study found teriparatide to offer more protection against fractures in women suffering from postmenopausal osteoporosis. Teriparatide is generally well-tolerated and rarely has side effects. The most common side effects it has includes injection-site pain and swelling (<3.3% of patients), nausea (8.5%), headaches (7.5%), leg cramps (2.6%), and dizziness (8%). There were no significant safety concerns mentioned by Han et al in their recent meta-analysis. Though, teriparatide has a limited use to 2 years because of the concern for human safety due to previous animal studies showing osteosarcoma related to teriparatide use beyond 3 years. Teriparatide is currently offered as a second-line treatment for the prevention of GIO due to its cost. Another drawback is its route of administration as a subcutaneous injection.

Because of the bone deterioration caused by glucocorticoid therapy prevention of bone fractures has significant importance. The bisphosphonates and other osteoporosis therapies don’t specifically target this mechanism. This leaves teriparatide as a more appealing approach. Teriparatide could have more significant therapeutic improvement of BMD and prevention of fractures resulting from long term glucocorticoid use, because of its mechanism of action. The purpose of this systematic review of the literature is to evaluate the efficacy of teriparatide in the prevention of fractures that can result from GC therapy.

METHODS

An extensive literature search was conducted using Medline-OVID, CINAHL, Evidence Based Medicine Reviews Multifile, and Web of Science using the search terms:
teriparatide, osteoporosis, fractures, and glucocorticoids. The search was narrowed to include English-language articles, human studies, and primary data. The reference sections of each of these articles were further searched for additional relevant sources. Inclusion criteria was based on adults who had a diagnosis of osteoporosis, were on glucocorticoid therapy, had a history of glucocorticoid-induced osteoporosis, had experienced fractures caused by glucocorticoid therapy, and were being treated with teriparatide therapy. Studies were excluded from this systematic review if they involved current treatment for another experimental drug or procedure. They were also excluded if they studied patients who were currently on or had been recently treated with a bisphosphonate. Articles were screened and evaluated for relevance using Grading of Recommendations, Assessment, Development and Evaluation (GRADE). 12

RESULTS

Using the search terms described in the previous section, the initial search yielded 18 articles for review. After screening relevant articles for human-studies and primary data, two articles met inclusion criteria. These two articles included a randomized, double-blind, control trial 13 and a randomized, control trial 14 (See Table 1).

Saag et al

This randomized, double-blind, double-dummy, active comparator-controlled trial 13 occurred over a period of 36 months in 13 countries at 76 centers comparing teriparatide with the antiresorptive drug alendronate (a Bisphoshonate) for treating
glucocorticoid-induced osteoporosis (GIO). There were 428 participants enrolled with osteoporosis (ages 22 to 89 years) and who had received glucocorticoids for at least 3 months (prednisone equivalent, 5mg daily or more). The study had three phases starting with a screening phase for 1.5 months, an 18 month primary phase, and a further 18 month continuation phase. The investigators and participants remained blinded throughout the course of the treatment for 36 months. The primary objective of the study was to investigate the change in BMD from baseline to 18 months between the teriparatide treatment group and the alendronate treatment group. Secondary objectives for the continuation to 36 months included evaluation of vertebral and nonvertebral fracture incidence.\textsuperscript{13}

Participants were eligible for enrollment if they were ambulatory men or women, at least 21 years of age, and they had taken prednisone or an equivalent at a dosage of greater than or equal to 5 mg per day for at least 3 months prior to screening. Each participant gave informed written consent, and an institutional review committee approved the protocol. The study was conducted under appropriate clinical guidelines in accordance with the Declaration of Helsinki and the Guidelines of Good Clinical Practice. The participants were also required to have a BMD T score of $<-2$ or of $<-1$ plus a low trauma or atraumatic fracture, for their lumbar spine, femoral neck, or total hip. Participants were randomly assigned to receive 20 $\mu$g of injectable teriparatide per day plus an oral placebo or 10 mg of oral alendronate per day plus an injectable placebo. Supplements of calcium and vitamin D were provided at dosages of 1,000 mg/day and 800 IU/day, respectively. The participants kept a daily diary of their glucocorticoid use. Baseline glucocorticoid use was determined by the duration and dosage of only the
glucocorticoids the participant was taking at study entry. Each visit had an average glucocorticoid dose determined by averaging the prednisone equivalent dose taken since the previous visit.13

Bone mineral density was measured using dual x-ray absorptiometry using Hologic (Hologic, Bedford, MA) or Lunar (General Electric Medical Systems, Madison, WI) densitometers. Bio-Imaging Technologies (Newport, PA) performed reading of the BMD scans, quality assurance, cross calibration adjustment, and data processing. Lumbar vertebrae that became fractured during the trial were excluded from the calculation of baseline and postbaseline lumbar spine BMD.13

There were also spinal radiographs obtained at baseline, at 18 months, and at 36 months. If there were symptoms suggestive of clinical vertebral fracture or other fracture symptoms experienced by participants, they were evaluated with spinal radiographs and radiographs of the other symptomatic areas. Regarding spinal compression fractures, each vertebra was graded for compression deformity by visual semiquantitative method using a Bio-Imaging Technologies radiologist who was blinded with regard to the treatment, but not to the sequence of radiographs. If there was an incident vertebral fracture discovered that was not fractured at baseline, it was subsequently graded as deformed. Also, if there were nonvertebral fractures, the radiologist was blinded to the treatment. This type of fracture was defined as a fracture associated with trauma equivalent to a fall from standing height or less, as assessed by the investigator.13

The analysis of the randomized subjects treated for BMD was conducted by means of a group comparison between baseline and end point. This involved using the
last observation carried forward method, which is defined at 36 months or at last postbaseline measurement with stratification variables as covariates using Analysis of Variance (ANOVA). By using a pre-defined gate-keeping strategy, overall Type I error was controlled at an alpha level of 0.05 for determining the earliest time at which the increase in BMD differed significantly between groups. If the 36-month comparison was significant at the 5% level then the 24-month comparison was tested, and this pattern was continued. This approach ensured that overall Type I error was not increased above the 0.05 level by testing at multiple time points. Testing of the remaining secondary outcomes, did not use adjustment for multiple comparisons.13

A within-treatment group post hoc analysis was used to determine whether percentage change in BMD was significantly different at successive time points. This was done using the mixed model with contrast. The covariates that were included were treatment, stratification variables, baseline lumbar spine BMD, time of appointment, and interaction between visit and treatment. There were additional subgroup analyses performed using ANOVA evaluating glucocorticoid dosage at baseline and 36 months, other musculoskeletal disease, respiratory disorders, and underlying conditions requiring glucocorticoids.13

Out of the 428 randomized subjects who received treatment, 150 (70%) of the subjects receiving teriparatide entered the 18 month continuation phase. Of those receiving alendronate 144 (67%) did so. Of the 150 treated with teriparatide, 123 (57%) completed the entire trial. Of the alendronate group, 118 (55%) participants continued to the completion. During these two phases, the most common reasons for discontinuation
in the study were subject decision and unspecified adverse event in both groups, with no significant difference between the treatment groups. There were more teriparatide subjects that discontinued due to physician decision and while more alendronate subjects were lost to follow-up.¹³

The differences in mean percentage in lumbar spine, total hip, and femoral neck BMD were greater in the teriparatide group than the alendronate group over the course of the trial from each time point until the end point. When comparing the teriparatide group to the alendronate group with regard to bone mineral density at 36 months, the mean percent increases from baseline were 11.0% versus 5.3%, respectively, for lumbar spine BMD (P < 0.001), 5.2% versus 2.7%, respectively, for total hip BMD (P < 0.001), and 6.3% versus 3.4%, respectively, for femoral neck BMD (P < 0.001). In the teriparatide group, the mean percent changes in BMD were significantly greater between the successive time points from 3 through 36 months at the lumbar spine, between 12 and 18 months and between 18 and 24 months at the total hip, and between 24 and 36 months at the femoral neck. In the alendronate group, the mean percent changes in BMD were significantly greater between 3 and 6 months, 6 and 12 months, and 18 and 24 months at the lumbar spine, between 12 and 18 months at the total hip, and between 12 and 18 months and 24 and 36 months at the femoral neck. The mean percent increases in BMD for both treatment groups were significant compared to baseline at each interval (P < 0.001 for teriparatide and P < 0.002 for alendronate, at all sites).¹³

There were no effects on BMD from underlying diseases that required glucocorticoid therapy. This was the same with regard to percentage change in lumbar
spine BMD from baseline to end point in both treatment groups. There was no significant difference across 4 underlying disease subgroups or across the 3 glucocorticoid dosage ranges.\(^\text{13}\)

With regards to incidence of vertebral and nonvertebral fractures, there were a total of 3 (1.7\%) of 173 subjects receiving teriparatide compared with 13 (7.7\%) of 169 subjects receiving alendronate had 1 new radiographic vertebral fracture over 36 months (\(P = 0.007\)). This had a relative risk of 22\% and a number needed to treat of 17 (See Table 1). Most of the vertebral fractures occurred during the first 18 months (1 within the teriparatide group and 10 with the alendronate group). There were no significant differences between groups in the number of subjects with new nonvertebral fractures or with new nonvertebral fragility fractures.\(^\text{13}\)

The authors admitted to some limitations including the 44\% dropout rate at 36 months, but failed to address the specific reasons. They concluded that teriparatide was superior to alendronate in both areas and that it should be considered a viable option for treatment GIO.\(^\text{13}\)

**Lane et al**

In this randomized, control study\(^\text{14}\) the authors conducted a 12 month clinical trial of human parathyroid hormone 1-34 (hPTH 1-34) in postmenopausal women with osteoporosis who were taking corticosteroids and hormone replacement therapy. Study subjects were selected as postmenopausal women between 50 and 82 years of age with a variety of chronic, noninfectious inflammatory diseases. They were eligible for the study if they had osteoporosis defined by a low bone mass (less than 2.5 standard deviations
below mean young normal values at the lumbar spine or femoral neck), had been menopausal for greater than or equal to 3 years, had been taking hormone replacement therapy (premarin or another estrogen at an equivalent dose) for greater than or equal to 1 year, had been treated with prednisone or an equivalent for the previous 12 months at a mean daily dose of 5.0 – 20.0 mg, and were expected to continue corticosteroid treatment for one year. Patients were excluded if they had a secondary form of osteoporosis other than one from rheumatic diseases and corticosteroids, renal or hepatic dysfunction, or abnormalities on spinal radiographs that precluded accurate measurements of the lumbar spine by quantitative computed tomography (QCT) or dual energy x-ray absorptiometry (DXA). The participants all gave informed consent and the study was approved by the Committee on Human Research of the University of California, San Francisco.\textsuperscript{14}

Fifty-one women who were postmenopausal and currently on estrogen and corticosteroids (CS) were randomly assigned by a computer generated table either to receive hPTH 1-34 plus estrogen (n=28), or to remain on estrogen only (n=23). The patients were given a calcium supplement of 1,500 mg per day and 800 IU of vitamin D3 supplement per day. The mean daily CS dose remained the same in the groups throughout the 12 month study period. Patients were taught subcutaneous self-injection by the research nurse at the start of the study. Placebo injections were not used. For 12 months hPTH 1-34 was at a dose of 25 µg (400 U) per day. Compliance was estimated by measuring the remaining volume in the returned medication vials at each study visit and ranged from 80 – 90% of the daily doses. Patients were evaluated at 1 month and then for every 3 months for 1 year to monitor the safety and efficacy of the treatment. Bone mass measurements of the lumbar spine by QCT were done from baseline and at 12
months. Bone mass measurements using DXA of the spine, hip, and forearm were performed every 6 months. Baseline DXA scans were obtained in duplicate and one every 6 months thereafter. The average of the baseline duplicate scan values was used in the analysis. Quality assurance data was collected daily from the DXA scanner to assess performance. Long-term in vivo precision error was 1.5% for the lumbar spine, 1.0% for the total hip region, 2.0% for the greater trochanter, 1.0% for the proximal or mid-forearm, and 3.0% for the distal 1/3 of the radius.14

Radiographs of the thoracolumbar spine were done annually by a standard technique to assess fractures at baseline and those during the course of the study. A new vertebral fracture was defined as a decrease of 20% and at least 4 mm in any vertebral height from baseline radiograph to that taken at completion of the study. Each fracture was confirmed by a repeat digitization of the involved vertebrae.14

Statistical analysis was performed looking at baseline differences between the groups. They were tested for significance with Student’s t test for normally distributed variables. Differences between the hPTH 1-34 plus estrogen group and estrogen-only groups during the course of the treatment were analyzed by repeated-measures using ANOVA. Tukey’s method was used for post-hoc analysis.14

The BMD of the lumbar spine measured by QCT and DXA increased significantly in the parathyroid plus estrogen group (P < 0.001) and remained the same in the estrogen only group. The mean differences between the treatment groups at 12 months (calculated by analysis of covariance) were 33.5% for the lumbar spine by QCT (P < 0.001) and 9.8% by DXA (P < 0.001). Compared to the spinal bone mass changes
with the hPTH treatment, there were only slight increases of 2.0% in the total hip, 2.9% in the femoral neck, and 1.3% in the greater trochanter. There was no significant decline in BMD at the spine or at the hip in the estrogen-only group. Bone mineral density of the forearm decreased about 1.0% in both groups during the 12 month study. There were no significant differences found between the groups with respect to BMD of the total hip, femoral neck, greater trochanter, or 1/3 distal radius at 6 and 12 months.¹⁴

No patients in the hPTH group (0/26) suffered a new vertebral fracture and one patient in the estrogen-only group (1/18) had evidence of a new vertebral fracture at the 12 month visit. This has a relative risk of 47% with a number needed to treat of 12 (See Table 1). During the treatment period, there were two patients in the hPTH plus estrogen group that had nonvertebral fractures (radius and pelvis) as did two patients in the estrogen only group (sacrum and rib).¹⁴

The authors felt that postmenopausal women with corticosteroid induced osteoporosis could benefit from daily subcutaneous injection of hPTH 1-34. No study limitations were addressed.¹⁴

DISCUSSION

These two studies¹³,¹⁴ demonstrate that teriparatide is an effective therapeutic option for patients with glucocorticoid-induced osteoporosis at high risk for fractures. Glucocorticoid therapy is beneficial for the treatment of chronic inflammatory, allergic, and inflammatory conditions. However, chronic use of GC therapy can lead to deterioration of the matrix in bone. Osteoporosis arises as a result of the side effects of long term
glucocorticoid use, which can be debilitating due to a reduction in bone mineral density,
leading to increased risk of fractures. Because of the effects of long term glucocorticoid
use, therapy is aimed at reversing the effects that result from GIO. Teriparatide has
beneficial effects of reversing the cause of GIO, however, it is often a second-line agent because
of its cost and route of administration being an injection, and its effect can vanish after a few
month or year once therapy is discontinued. It is also limited on its use to 2 years because of the
concern for human safety due to previous animal studies showing osteosarcoma related to
teriparatide use beyond 3 years.

Teriparatide is a more beneficial alternative to the bisphosphonates because of having a
considerably improved BMD and lower incidence of fractures. Due to teriparatide’s anabolic
activity, bone health in patients with GIO can be stabilized to avoid deterioration, prevent
fractures, and to improve a GIO patient’s quality of life. A meta-analysis of randomized control
trials by Han et al determined teriparatide to substantially reduce the risk of fragility fracture in
postmenopausal women with a 70% reduction in vertebral fracture and a 38% reduction in non-
vertebral fracture. The EFOS study showed that teriparatide has an immediate and long
lasting effect, reducing the occurrence of clinical fractures both during treatment and
after treatment. Teriparatide has also been found to offer more protection against fractures
significantly in women suffering from postmenopausal osteoporosis. Based on the
pathophysiology of bone degeneration caused by GIO, it has been recommended that
pharmacologic agents that stimulate bone formation and accelerate remodeling (most
significantly in trabecular bone of the lumbar spine), such as teriparatide, may be the
more appropriate treatment option over antiresorptive agents for patient with GIO at high
risk for fractures, which was also a conclusion by Lane et al. Because of its efficacy
over bisphosphonates in improved bone mineral density and reduced fracture rates, teriparatide
should be considered as a first line option for the treatment of glucocorticoid-induced osteoporosis.

After evaluation of a randomized, double blind, control trial of subjects receiving teriparatide in comparison to subjects receiving alendronate, there were significantly greater increases in spine and hip BMD, and fewer new vertebral fractures, in those receiving teriparatide over a 36 month time period. In comparing BMD changes, there was an increase of 11% versus 5.3% for L-Spine, 5.2% versus 2.7% for total hip, and 6.3% versus 3.4% for femoral neck (P < 0.001 for all). This shows considerable benefit of teriparatide as its BMD improvement is nearly double to that of alendronate in patients with GIO. The trial also shows efficacy of reduced incidence of fracture in those receiving teriparatide. For example, in the teriparatide group there were 3 new radiographic fractures out of 173 participants, versus 13 out of 169 participants in the alendronate group over a 36 month period. The relative risk for this was 22% and the number needed to treat was 17 (See Table 1). Fracture incidence is significantly lower in the teriparatide group, suggesting that its effects could be therapeutically superior to alendronate in preventing the occurrence of fractures. The authors also avoided inaccuracies using approaches such as daily diaries made by the participants of their glucocorticoid use and compliance with usage of the drugs being compared. It was noteworthy that mean percent changes in BMD were significantly highest and changed the earliest in the lumbar spine region (at 3 mos.), since this is the area of bone that can have the first signs of GIO and most likely to experience fractures. There was improvement in the total hip (18 mos.) and femoral neck (24 mos.) much later than the lumbar spine, which is significant since the fracture occurrence in this study was highest.
in the first 6 months. Therefore, clinical application of teriparatide can help avoid spinal fractures faster since it showed improvement in BMD within the first 3 months. Patients that are at high risk of deterioration and fracture associated with long term glucocorticoid use, can have significantly greater benefit in improved BMD in the spine, hip, and femoral neck, as well as a lower likelihood of vertebral fracture, if they are placed on teriparatide over alendronate.

Lane et al\textsuperscript{14} evaluated how postmenopausal women taking stable, low doses of chronic glucocorticoids and estrogen supplementation could have changes in bone mineral density when placed on hPTH 1-34. The treatment with hPTH 1-34 in these subjects showed a dramatic increase of bone mass in spinal trabecular bone and integral bone, as well as minimal increases of bone mass in the bones of the hip and forearm.\textsuperscript{14} This is again, suggestive that teriparatide helps the bones that are most affected by GIO, which was also evident in the work performed by Saag et al.\textsuperscript{13} None of the patients in the hPTH group suffered a new vertebral fracture, while there was one in the estrogen-only group over the 12 month study period. Between the two groups, there were four non-vertebral fractures over the 12 month period. This shows a relative risk of 47\% with a number needed to treat of 12 (See Table 1). There was also no evidence of harmful or adverse effects from the hPTH 1-34 treatment. This improved bone mass from administration of hPTH 1-34 provides reasonable evidence for reversing the effects of GIO and preventing the occurrence of fractures.

While the studies\textsuperscript{13,14} of this systematic review demonstrated teriparatide to be effective for improving BMD and reducing fracture incidence, they each have their
limitations. The randomized, double blind, control trial by Saag et al\textsuperscript{13} was of moderate quality with a serious limitation being from a high attrition rate of 44\% at the completion of 36 months. The authors noted that the most common reason for study discontinuation were by physician decision and adverse events.\textsuperscript{13} However, they failed to describe or discuss the specifics of what those adverse events were that could have lead to the high attrition rate. This is concerning since it would be important to know what those specific adverse events were if it they can be attributed to safety concerns. It is possible, that the high attrition rate of the study subjects could have been due to the severity of underlying diseases associated with treatment of glucocorticoids, as well as resulting from other comorbid conditions. There could have been inconsistencies due to the locations of the study, as it spanned across 13 countries and was not limited to the United States. There was also a lack of precision due to a small sample size. This was the same case for the study by Lane et al\textsuperscript{14} which had only 28 people in the teriparatide treatment group and 20 in the control group.

Lane et al\textsuperscript{14} studied only female patients that were postmenopausal between the ages of 50-82 further limiting the applicability of the study. This study also discussed the use of radiographs to evaluate the presence of fractures, but was not clear on when those radiographs occurred. They described them as annual, but also wrote that radiographs were taken at 6 and 12 months. The authors of this study also had no discussion of any limitations they experienced or in their methodology. The evidence yielded by Lane et al\textsuperscript{14} was of moderate quality which was negatively affected by small sample size and had a serious limitation of not being blinded.
These studies\textsuperscript{13,14} answer the question regarding teriparatide for the prevention of fractures in patients with GIO. The study by Saag et al\textsuperscript{13} had a number needed to treat of 17 and the study by Lane et al\textsuperscript{14} had a number needed to treat of 12. Both studies also had results of improved bone mineral density in subjects with GIO who were treated with teriparatide. There is little doubt that teriparatide is a useful treatment option for GIO, even given that the quality of evidence from this systematic review has revealed significant limitations to the studies.

CONCLUSION

Teriparatide is well tolerated offering therapeutic efficacy of improved BMD and should be considered for protection against fractures resulting from glucocorticoid-induced osteoporosis. It has shown improvement more significantly than bisphosphonates when treating the effects of GIO as well as preventing the incidence of fractures. The data of teriparatide therapy overall make it an efficacious treatment option for GIO and other forms of osteoporosis, when compared to other therapies. Teriparatide therapy by daily subcutaneous injection can result in lower incidence of GIO effects after initiation of therapy and continues to prevent the effects of GIO once therapy has stopped. When combining the quality of studies reviewed, the overall quality is moderate according to the GRADE criteria (See Table 1).

It is still important to consider further research for the use of teriparatide treatment in a variety of causes of osteoporosis as well as the possibility of refining it to be safer for humans beyond 2 years. Because of the concern raised by the work of Saag et al\textsuperscript{12} of no definitive reason for what the adverse events were, research aimed at the safety of teriparatide use for GIO and other forms of osteoporosis in randomized control trials would be more convincing that it is a safe
therapeutic option. Further randomized control trials with a larger study population including men and women with GIO, or other forms of osteoporosis, looking at improved BMD and reduction of fracture incidence would also benefit decision making for teriparatide as a treatment option. There could also be more randomized comparative studies with bisphosphonates and other osteoporotic medications using a larger, more diverse patient population to see how teriparatide’s efficacy measures up as a go to treatment option for prevention of fractures. While further research could significantly benefit the understanding, effectiveness, and safety of teriparatide, it has proven to significantly benefit the BMD bones that are most effected by GIO as well as being a preventative measure for avoiding fractures that result from GIO.

Though the cost and limited time of applicability for teriparatide treatment may steer one away from using teriparatide for treating GIO and other forms of osteoporosis, it has a mechanism of action that has proven to significantly improve BMD and prevent fractures both after initiation of therapy and for some time once it is discontinued.
References


There was a small number of patients who were studied for fracture rates (28) and an attrition rate of 44% over the 36 month time course. There was no blinding used in the study.

Bone mineral density was measured by percentage change using dual x-ray absorptiometry or quantitative computed tomography (QCT) or dual-energy x-ray absorptiometry (DXA).

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Table 1 - GRADE Evidence Profile: Teriparatide for prevention of fractures in patients with glucocorticoid-induced osteoporosis.
Figure 1. Pathophysiology of Glucocorticoid-induced Osteoporosis Leading to Fractures

- **Oral GCs**
  - ↓Osteoblast differentiation and activity.
  - ↑Osteocyte Apoptosis
  - ↓Production of estrogens (women) and testosterone (men)
  - Muscle Weakness and Atrophy
  - ↑Risk of Fracture

- **↑Risk of Fracture**
  - ↑Likelihood of falling
  - ↓Bone Formation
  - ↓Bone Architecture and Quality
  - ↓BMD
  - ↓Bone Formation
  - Negative Calcium Balance