

Anabolics in the management of glucocorticoid-induced osteoporosis: an evidence-based review of long-term safety, efficacy and place in therapy

This article was published in the following Dove Press journal:
Core Evidence

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Introduction: Glucocorticoid-induced osteoporosis is an underrecognized complication of chronic glucocorticoid therapy characterized by a decrease in new bone formation. Anabolic therapies, such as teriparatide, a recombinant human parathyroid hormone, combat the disease by promoting new bone growth.

Aims: This article outlines the pathophysiology of glucocorticoid-induced osteoporosis and details the evidence of efficacy, safety, and patterns of use of teriparatide and other future anabolic therapies.

Evidence review: In multiple clinical trials, teriparatide has been shown to significantly increase lumbar spine bone mineral density (BMD) in patients with glucocorticoid-induced osteoporosis when compared with placebo, alendronate, and risedronate. When compared with alendronate, significantly fewer vertebral fractures were noted in the teriparatide group. Adverse effects noted in clinical trials include nausea, insomnia, flushing, myalgias, and mild hypercalcemia/hyperuricemia. Early studies in rats noted an increased incidence of osteosarcoma; however, an increased rate beyond levels seen in general populations has not been noted in human studies or with long-term pharmacovigilance. Abaloparatide and romosozumab are newer anabolic therapies that have shown some benefit in postmenopausal osteoporosis but have not yet been studied in the chronic glucocorticoid population.

Place in therapy: Major specialty organizations continue to recommend bisphosphonates as first-line therapy in glucocorticoid-induced osteoporosis due to the proven benefit and relative affordability. However, the use of anabolics shows promise to improve outcomes by increasing BMD and reducing fracture-associated morbidity and mortality and has a role for selected populations at high fracture risk.

Keywords: teriparatide, steroid, osteoporosis, GIOP

Core evidence clinical impact summary for teriparatide

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Outcome measure	Evidence	Implications
Disease-oriented evidence	Clinical trials	Teriparatide has been shown to increase BMD and decrease fractures compared to alendronate in patients with GIOP.

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Outcome measure	Evidence	Implications
Patient-oriented evidence	Clinical trials	Teriparatide is generally well tolerated. Initial concerns of osteosarcoma risk have not been observed to date at a greater rate than seen in general populations not on teriparatide. Effects of teriparatide on health-related quality of life have not been well documented in this patient population.
Economic evidence	Cost-effectiveness analysis	Teriparatide is more expensive than bisphosphonates, but limited data on cost-benefit suggest that among patients at high risk for fracture on glucocorticoids, teriparatide may be below societal thresholds for typical health care programs considered cost-effective.

Scope of the problem

Glucocorticoid-induced osteoporosis remains an underrecognized problem in patients receiving long-term glucocorticoid therapy. Despite the emerging number of glucocorticoid-sparing therapies, physicians and patients still rely on glucocorticoids in the management of many acute and chronic illnesses.¹ A study of patients registered with a general practitioner in England noted that glucocorticoids are used chronically by 0.5% of the population, including 1.4% of patients older than 55 years.² A more recent analysis placed the prevalence of glucocorticoid use in 1 year at 3%, which was stable to slightly increased from a prior study in 1999.³ A third study noted a 34% increase in long-term glucocorticoid use from 1989 to 2008.⁴ While the risks of long-term glucocorticoid use on bones are well known, they remain underrecognized and undertreated.⁵ One study looking at new glucocorticoid prescriptions found that only 41% of women older than 50 were prescribed concurrent antiosteoporotic therapies and only 16% had a bone mass measurement.⁶

Mechanism of glucocorticoid effects on bone

The pathophysiology of glucocorticoid-induced osteoporosis arises primarily from the direct effects of glucocorticoids on bone and is characterized by two distinct phases: an early rapid and transient phase followed by a slower, progressive phase.⁷ The early phase is primarily characterized by an

increase in osteoclastogenesis that leads to an increase in bone resorption. This effect is mediated by an upregulation of receptor activator of nuclear factor kappa-B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) along with a decrease in osteoprotegerin (OPG).^{8,9} However, this effect is only temporary; the primary driver of glucocorticoid-induced osteoporosis is mediated by a reduction in the number of circulating osteoblasts. This is accomplished by several different pathways. Glucocorticoids upregulate the expression of peroxisome proliferator-activated receptor-gamma (PPAR- γ), which subsequently increases the differentiation of precursor cells to adipocytes rather than osteoblasts, thereby decreasing the number of circulating osteoblasts.¹⁰ Next, osteoblastogenesis is mediated by the Wnt/ β -catenin signaling pathway. However, glucocorticoids inhibit Wnt binding via increased expression of Dickkopf1 (Dkk1), subsequently inducing destabilization of β -catenin by glycogen-synthase kinase-3 β and a resulting decrease in osteoblastogenesis.^{11–17} Finally, activation of caspase 3 leads to increased apoptosis of circulating osteoblasts.^{18,19}

Epidemiology of glucocorticoid effects on bone

It is well established from epidemiologic studies that long-term glucocorticoid use has a negative effect on bone health. Several studies have noted an increased risk of fractures among patients on chronic steroid therapy.^{20–25} This risk appears to be dose dependent, both with the daily dose and

with cumulative dose, and at least partially reversible upon cessation of steroid use.^{20,23,26} However, many patients with rheumatoid arthritis, the most common glucocorticoid-requiring disease, still use small doses to control disease despite being on steroid-sparing therapy, and increased fracture risk has been seen even at small daily doses.^{1,23}

As discussed above, glucocorticoid use causes a rapid increase in bone resorption followed by decreased formation of new bone that has a significant effect on overall bone health. A study of a Norwegian cohort found that current glucocorticoid usage was associated with a 2.6-fold decrease in bone mineral density (BMD) when followed over 2 years.²⁷ Steroid use also has negative consequences on bone health independent of BMD; a study in postmenopausal women noted an increased risk of fracture at similar BMD in patients on chronic steroid therapy.²⁸ The effect of steroids on bone health seems to be at least partially reversible on discontinuation of the drug, but this is not an option for all patients, necessitating adequate antiosteoporotic therapy.²⁹

Antiresorptive therapies in glucocorticoid-induced osteoporosis

Bisphosphonates are the best-studied drug class in the treatment of postmenopausal osteoporosis, and this has largely carried over to glucocorticoid-induced osteoporosis as well. Alendronate, risedronate, raloxifene, and ibandronate have all been shown in randomized controlled trials to increase BMD over placebo in glucocorticoid-induced osteoporosis.^{30–35} Zoledronic acid and denosumab have been shown to be superior to risedronate in BMD increase.^{36,37} Finally, risedronate and alendronate have been shown to decrease vertebral fracture rate compared to placebo, based on extensions to clinical trials or post hoc analyses of the original trials.^{38,39}

Anabolic therapies in glucocorticoid-induced osteoporosis – mechanism and overview

Despite the proven efficacy of the antiresorptive therapies above, bisphosphonates may not be the ideal treatment for osteoporosis caused by long-term steroids, particularly within the low-turnover state of the disease. The chronic long-term effects of steroids on the bones are mediated by a decrease in bone formation, due to the decrease in osteoblast production and activity. Thus, strictly antiresorptive therapy may not be as beneficial in this low-turnover state as in osteoporosis secondary to estrogen deficiency, a high turnover state mediated by a relative increase in osteoclast

activity.⁴⁰ Anabolic therapies protect against bone degradation by promoting new bone growth rather than by a reduction in remodeling. This is accomplished by reversal of many of the pathways, leading to glucocorticoid-induced osteoporosis as noted above, including enhancement of the Wnt signaling pathway and inhibition of PPAR-gamma, ultimately leading to increase in circulating osteoblasts.⁴¹ The concept of an “anabolic window” has been described in which direct action on osteoblasts leads to a rapid but short-lived period of increased bone growth. This is then followed by a second, less rapid phase of bone growth.

Teriparatide in glucocorticoid-induced osteoporosis BMD and fracture data

Teriparatide, a subcutaneous recombinant human parathyroid hormone (1–34), was the first anabolic agent approved for the treatment of osteoporosis and the only one that has been studied specifically in glucocorticoid-induced osteoporosis. Before being approved for patients on chronic glucocorticoid therapy, PTH and teriparatide were tested in postmenopausal women and men with osteoporosis prior to receiving FDA approval for these indications in 2002. A randomized controlled trial conducted in 2001 on postmenopausal women with osteoporosis noted a decreased fracture risk and increased BMD in the lumbar spine and femoral neck in patients on teriparatide when compared with placebo.⁴² A smaller RCT in 2002 conducted in postmenopausal women showed a significant increase in BMD at the lumbar spine, femoral neck, and total body, as well as a reduced nonvertebral fracture rate, in patients treated with teriparatide compared to those treated with alendronate.⁴³ A third RCT conducted in 2003 in men with osteoporosis noted an increase in femoral neck, spine, and total body BMD in the teriparatide group compared to the placebo group.⁴⁴

The first study of PTH in glucocorticoid-induced osteoporosis was a randomized controlled trial in 1998.⁴⁵ The study was conducted in 51 postmenopausal women with 12 months of previous steroid use and compared hormone replacement therapy with hormone replacement therapy plus PTH. The primary endpoint of the study was BMD at the lumbar spine, which, after 12 months of therapy, was significantly higher in the PTH group (35% and 11% by quantitative CT and dual-energy X-ray absorptiometry [DXA], respectively) than in the estrogen-only group (1.7% and 0%, respectively). No significant differences

were seen in BMD at the total hip or femoral neck between the two groups, and the study was not powered to detect differences in fracture rates.

The landmark trial in teriparatide use in glucocorticoid-induced osteoporosis was published in 2007.⁴⁶ The study was a large, multicenter, randomized controlled trial testing teriparatide against alendronate in patients with glucocorticoid-induced osteoporosis. Participants in the trial were patients 21 years of age or older with a history of sustained glucocorticoid therapy (defined as the mean daily dose of prednisone 5 mg or more for at least three consecutive months) with a T score of -2.0 or -1.0 and a history of a fragility fracture while on steroids. Participants were divided into groups of daily 20 mcg teriparatide or daily 10 mg oral alendronate for 18 months. The primary endpoint of the trial was BMD of the lumbar spine and total hip, assessed by DXA. Additional endpoints included fractures, divided into vertebral and non-vertebral, and markers of bone remodeling. After 18 months of therapy, the teriparatide group had a 7.2% increase in lumbar spine BMD vs 3.4% in the alendronate group ($p < 0.001$) and the teriparatide group had a 3.8% increase in total hip BMD vs 2.4% in the alendronate group ($p = 0.005$). Vertebral fractures were significantly decreased in the teriparatide group; there were no significant differences in nonvertebral fractures between the two groups. Adverse events were minor and relatively similar between the two groups. The trial was continued through 36 months with similar results with a significant increase in lumbar spine, total hip, and femoral neck BMD in the teriparatide group as compared to the alendronate group. The teriparatide group had fewer vertebral fractures; there was no difference in nonvertebral fractures.⁴⁷ Results from the trial are summarized in [Figure 1](#).

A third large randomized controlled trial, the EuroGIOPs trial published in 2013, pitted teriparatide vs risenedronate in men with glucocorticoid-induced osteoporosis.⁴⁸ In the primary outcome of this trial, after 18 months, lumbar spine BMD, as measured by quantitative computed tomography (QCT), demonstrated a 16.3% increase in the teriparatide group vs a 3.8% increase in the risenedronate group ($p = 0.004$). New clinical fractures were fewer in the teriparatide group (zero as compared to five in the risenedronate group), but the difference was not statistically significant ($p = 0.056$).

Bone turnover markers and alternative endpoints

Bone turnover markers (BTMs) provide a convenient way to analyze the different mechanistic effects of anabolic

therapies compared to antiresorptive therapies and are another surrogate measure for a biologic response. An increase in bone formation markers has been consistently noted in studies with teriparatide, in opposition to the decrease in bone formation markers seen in bisphosphonates such as alendronate/risenedronate.⁴⁵⁻⁵⁰ Changes in procollagen type I N propeptide (PINP), a protein formed during the synthesis of new type I collagen in the osteoblast, have been noted to correlate with increases in BMD as well as changes in finite element strength in patients on teriparatide.^{50,51}

As imaging techniques improve, more sensitive techniques to quantify bone strength have been developed and used in the study of teriparatide. High-resolution computed tomography (HRCT) is one such emerging alternative method to measure BMD.⁵² While BMD is most widely measured using DXA, HRCT uses three-dimensional imaging to permit greater sensitivity in diagnosis as well as the ability to measure both cortical and trabecular bone integrity. As noted above, this technique was applied in the EuroGIOPs trial where teriparatide was compared with risenedronate in men with glucocorticoid-induced osteoporosis.⁴⁸ Teriparatide was noted to have greater BMD at the lumbar spine, as measured by QCT as well as improved bone strength and stiffness, calculated by HRQCT-based finite element analysis, a model used to simulate the properties of bone.⁵³

Reference point indentation is a technique in which the mechanical properties of a bone can be analyzed at a level of detail finer than exclusively imaging-based tests. As previously noted, patients on long-term glucocorticoids are at increased risk of fractures compared to controls with similar BMD measurements, indicating that glucocorticoid use causes a deterioration in bone quality not adequately measured by BMD. A study evaluating reference point indentation in patients recently starting glucocorticoids noted a significant decrease in bone material strength index (BMSi) in patients on calcium/vitamin D only, no significant change in patients on risenedronate, and an improved BMSi in denosumab and teriparatide after 7 weeks of therapy. No BMD changes were noted over this period, indicating that reference point indentation provides the sensitivity necessary to detect early changes in bone integrity not seen on traditional imaging measures.⁵⁴

The trabecular bone score (TBS) is a technique to assess the bone texture and provide information about bone quality from DXA images. TBS has been positively correlated with bone microarchitecture and is a better

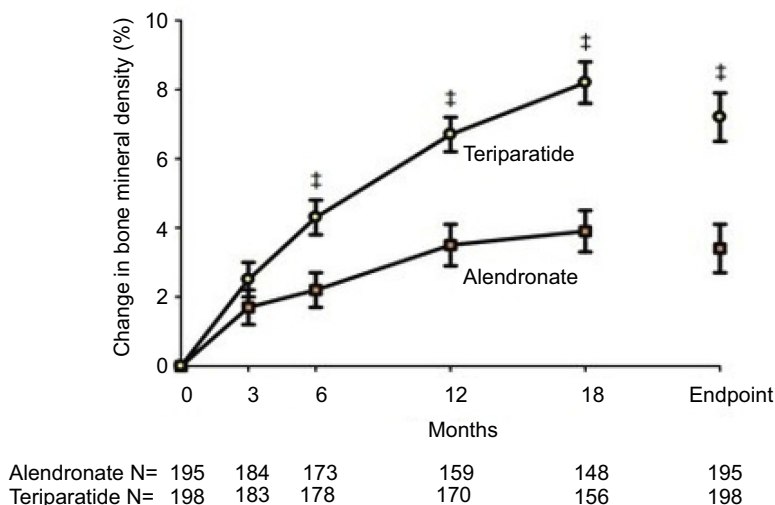
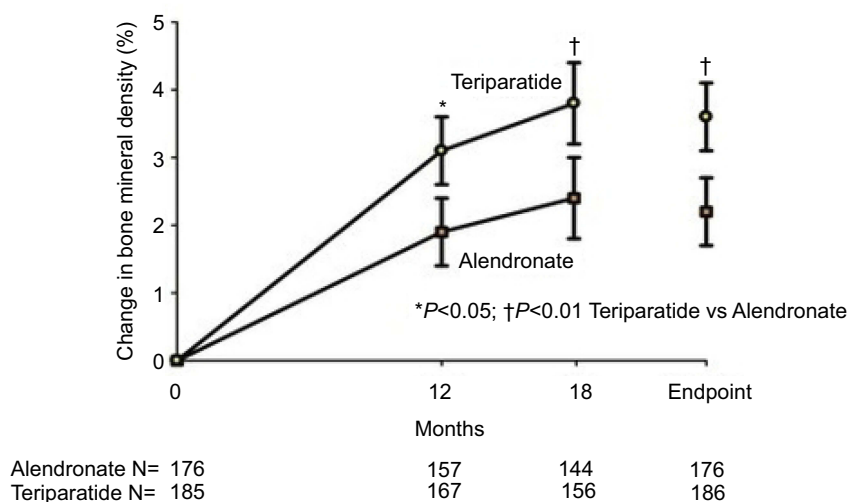
A Lumbar spine**B** Total hip

Figure 1 Results of a randomized-controlled trial comparing teriparatide with alendronate in patients with glucocorticoid-induced osteoporosis.

Note: From the *New England Journal of Medicine*, Saag KG, Shane E, Boonen S, et al, Teriparatide or Alendronate in Glucocorticoid-Induced Osteoporosis, 357(20), 2028–2039, Copyright © 2007 Massachusetts Medical Society. Reprinted with permission.⁴⁶

predictor of fracture risk than BMD.^{55,56} A subpopulation analysis of the original teriparatide vs alendronate trial used archived DXA scans to calculate TBSs in order to compare the effects of teriparatide and alendronate on TBS as well as assess for differences between BMD and TBS. As noted above, the BMD increased in both groups from baseline; however, only the teriparatide group noted a significant increase in TBS from baseline, while the alendronate group noted no significant difference in TBS.⁵⁷ This finding indicates that the TBS may be another sensitive measure that can detect differences and effects of treatment better than BMD alone.

Safety

The safety of teriparatide has been a topic of potential concern since the initial study and development of the drug. In the large RCTs referenced above, teriparatide tended to be well tolerated, with only minor side effects such as nausea, insomnia, flushing, myalgias, and mild hypercalcemia/hyperuricemia.^{46,48} However, early rat studies indicating an increased risk of osteosarcoma and other bone tumors have necessitated further study on the safety of the drug.⁵⁸ Due to these findings, the FDA mandated a postmarketing study to further study this association. In 2012, the 7-year findings of this 15-year study were

published, and it was noted that no patients had developed osteosarcoma with a prior history of teriparatide use.⁵⁹ Data presented from the 12-year follow-up noted two patients who had developed osteosarcoma following teriparatide treatment. This rate was deemed to be within the expected range assuming no increased risk.⁶⁰ The difference in findings in rat and human studies may be due to different patterns of use, since rat studies noting increased osteosarcoma risk have either been at much higher doses or for a much longer relative duration than are typically used in humans.^{61–63}

Furthermore, bisphosphonates are not without safety risk either. Long-term use of bisphosphonates can impair the bone quality and has been associated with osteonecrosis of the jaw and atypical fractures, among others.^{64,65} Like any medication, caution should be taken when long-term use of a medication is anticipated.

Cost

A final concern that may potentially limit the widespread use of teriparatide in glucocorticoid-induced osteoporosis is the cost of the medication. Indeed, teriparatide is significantly more expensive than bisphosphonates, and patients with glucocorticoid-induced osteoporosis typically have an underlying medical condition that would make affordability even more of a concern. However, given the decrease in vertebral fractures associated with teriparatide, leading to direct cost savings, as well as improvement in the quality of life, a justification could be made for the long-term cost-effectiveness of teriparatide. One economic analysis found that when the additional mortality from osteoporosis-related fractures was considered, teriparatide could be economically justified as first line for glucocorticoid-induced osteoporosis.⁶⁶

Patterns of use

Because teriparatide currently has a limited time course, the question of whether bisphosphonates are beneficial following a course of teriparatide therapy was an important topic of study. Although not done specifically in glucocorticoid-induced osteoporosis, the PaTH study published in 2005 randomly assigned patients who previously underwent 1 year of PTH to placebo or alendronate.⁶⁷ After 1 year, the patients in the alendronate group noted a significant increase in gains in BMD at both the spine and hip. Based on these findings and other studies, nearly all patients who receive anabolic agents should follow these drugs with antiresorptive therapy to maximize the

benefits and to “fill-in” the new remodeling space collected. Simultaneous bisphosphonates with PTH, tested earlier in the same trial, appeared to blunt the effect of PTH rather than the enhancement seen by sequential therapy.⁶⁸

The optimal duration of teriparatide treatment is not completely clear. Currently, due to concerns about safety, a maximum of 24 months of therapy is recommended. Teriparatide appears to provide benefit beyond this time-frame; the 36-month follow-up of the original teriparatide-alendronate trial noted a significant increase in BMD between months 24 and 36 with minimal difference in adverse events; however, further study is needed.⁴⁷

Similarly, the benefit of a second course of therapy after a discrete break has mixed results. Two studies published in 2009 measured the effects of retreatment with teriparatide. The first enrolled patients who had previously completed 1 year of teriparatide and then 1 year of alendronate and treated them with an additional year of teriparatide.⁶⁹ Similar BMD increases were seen after each course of teriparatide, drawing the conclusion that retreatment may be a viable option. However, a separate study in which teriparatide was taken for a year, stopped for a year, and then taken for an additional year found an attenuated effect in BMD increase on the second course of teriparatide.⁷⁰ Additional study is needed to determine the benefit of a second course of medication.

Other anabolic therapies in glucocorticoid-induced osteoporosis

Anabolic sex steroids

Prior to the discovery of PTH and teriparatide, anabolic sex steroids and hormone replacement therapy were a topic of study in glucocorticoid-induced osteoporosis. Sex steroids were an appealing target for therapy; the rationale being that long-term glucocorticoids led to a sex corticosteroid deficiency, which then resulted in increased bone reabsorption, and HRT was familiar from its popularity at the time in treatment of postmenopausal osteoporosis.⁷¹ In women on long-term glucocorticoids, hormone replacement therapy demonstrated significant increases in BMD and decreased bone resorption.^{72–74} Enthusiasm for the use of HRT in glucocorticoid-induced osteoporosis diminished after the publication of the Women's Health Initiative (WHI) trial exposed the risks of long-term HRT.⁷⁵ Androgen supplementation with nandrolone decanoate in women with glucocorticoid-induced

osteoporosis was showed to increase forearm bone density.⁷⁶ Finally, testosterone supplementation in men on chronic glucocorticoid therapy was associated with increase in BMD at the lumbar spine and hip.^{77,78} No benefit was seen with nandrolone decanoate in men.⁷⁸

Abaloparatide

Although teriparatide is the only anabolic antiosteoporotic therapy that has been specifically studied in a long-term glucocorticoid population, there is emerging evidence supporting the study of additional medications with similar mechanisms of action. Use of abaloparatide, a daily subcutaneous parathyroid hormone-related protein analog, in postmenopausal women has demonstrated significantly increased BMD at the lumbar spine, femoral neck, and total hip when compared to placebo as well as a significantly reduced incidence of both vertebral and nonvertebral fractures at a wide range of baseline fracture risks.^{79–83} Efficacy was mostly comparable to teriparatide in limited trials, although abaloparatide was associated with a significant increase in total hip BMD compared to teriparatide.⁷⁹ The mechanism behind this difference is unclear but may be due to a decreased bone resorption period, leading to a larger increase in bone growth.⁸⁴

Romozosumab

Romozosumab is a monoclonal antibody against sclerostin, a protein secreted by osteocytes that inhibits bone formation through regulation of osteoblasts. Like abaloparatide, sclerostin antibodies have not been studied in patients on chronic steroids; however, they have shown benefit when administered subcutaneously in postmenopausal women and men. In postmenopausal women specifically, romozosumab increased BMD when compared to placebo and teriparatide and decreased the incidence of fractures when compared to placebo and alendronate.^{85–89} Fewer data exist in men, but a Phase III trial noted an increased spine and hip BMD in romozosumab when compared to placebo.⁹⁰

Organizational glucocorticoid-induced osteoporosis guidelines

Different major specialty organizations have published guidelines regarding the use of teriparatide in the treatment of glucocorticoid-induced osteoporosis. The International Osteoporosis Foundation and the European Calcified Tissue Society (IOF-ECTS) published a set of guidelines

in 2012, where they mentioned teriparatide as a frontline option, along with alendronate, etidronate, risedronate, and zoledronic acid.⁹¹ They reviewed the data included above but did not differentiate among the medications listed as frontline. The UK National Osteoporosis Guideline Group (NOGG) and the American College of Rheumatology (ACR) both published guidelines in 2017.^{92,93} The NOGG gave teriparatide an A-grade recommendation based on proven benefit in spine BMD, hip BMD, and vertebral fracture but recommend alendronate and risedronate as first line due to lower cost, mentioning that teriparatide can be considered if these are not tolerated or contraindicated. The ACR took a similar stance, recommending oral bisphosphonates over teriparatide in adults at moderate and high risk of major fracture due to the cost and burden of therapy with daily injections. In patients who have a new fracture or significant worsening of BMD on oral bisphosphonates, the ACR recommended consideration of teriparatide at that time.

Conclusion

Glucocorticoid-induced osteoporosis is an underrecognized complication of chronic steroid therapy. The underlying mechanism of disease, that of a low-turnover state characterized by a decrease in the formation of new bone, differs from that of postmenopausal disease, and the optimal treatment of the disease may differ as well. Anabolics, such as teriparatide, a recombinant parathyroid hormone, offer a way to increase bone production in a way that traditional antiresorptive therapies do not. The optimal treatment course and long-term effects are still under investigation, but teriparatide therapy appears to improve bone quality and decrease fracture risk when compared to antiresorptive therapy. Future directions include investigations into new anabolic medications, head-to-head comparisons between anabolics, as well as more study on the optimal duration of anabolic therapy and the potential for repeated courses of therapies.

Disclosure

Kenneth G Saag reports personal fees from Abbvie, Amgen, Ironwood/AstraZeneca, Bayer, Gilead, Horizon, Kowa, Radius, Roche/Genetech, SOBI, Takeda, and Teijin; and grants from Amgen, Ironwood/AstraZeneca, Horizon, SOBI, Takeda, Radius, and Mereo, outside the submitted work. Kenneth G Saag has served as a consultant to Amgen, Radius and Roche. The authors report no other conflicts of interest in this work.

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