Review

Anabolic treatment for osteoporosis and fragility fracture risk: one year in review 2024

G. De Mattia, M. Maffi, M. Mazzantini

Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Italy

Giammarco De Mattia, MD
Michele Maffi, MD
Maurizio Mazzantini, MD

Please address correspondence to:
Giammarco De Mattia
U.O. di Reumatologia, Azienda Ospedaliero Universitaria Pisana, via Roma 67, 56126 Pisa, Italy.
E-mail: dr.g.demattia@gmail.com

Received on April 27, 2024; accepted in revised form on July 8, 2024.

Clin Exp Rheumatol 2024; 42: 1311-1316.

Key words: osteoporosis, fragility fracture, abaloparatide, trabecular bone score, sequential therapy

Competing interests: none declared.

ABSTRACT

Osteoporosis is a skeletal disease characterised by reduced bone mass and deterioration of bone microarchitecture, underlying a higher risk of fragility fractures. Several options are available for its treatment, including both anti-resorptive and anabolic agents. The present review discusses and summarises the most recent literature on anabolic treatment, with a focus on abaloparatide, and on the assessment of fragility fracture risk, with a focus on trabecular bone score. Finally, we provide a discussion on the effects of different anti-osteoporotic medications in terms of fragility fracture risk reduction.

Introduction

Osteoporosis (OP) is a progressive skeletal disease characterised by reduced bone mass and deterioration of bone architecture; it is especially prevalent among postmenopausal women and the elderly population. Fragility fractures (FFs) are a major complication of OP and may result in low quality of life along with increased morbidity and mortality (1). Much effort has been made over the last two decades to develop new anti-osteoporotic medications (AOMs) and to accurately predict the individual risk for FFs and drive treatment accordingly. The present paper tackles the most relevant contributions published throughout 2023 on the evaluation of FF risk, including trabecular bone score (TBS), and on anabolic treatment of OP, with a special focus on abaloparatide (ABL).

Abaloparatide: overview and key findings of 2023

Several AOMs are available nowadays for the treatment of OP. Anti-resorptive agents comprise bisphosphonates (BPs), menopausal hormone therapy (MHT), selective estrogen receptor modulators (SERMs) and denosumab, whereas anabolic agents include the parathyroid hormone (PTH) analogues teriparatide (TPTD) and abaloparatide (ABL), and the anti-sclerostin antibody romosozumab, which features also an anti-resorptive effect (2).

ABL is the second PTH-like agent after TPTD to be approved for the treatment of OP following the results observed in an international, randomised, placebo- and active-controlled trial, called The Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE), in which 2463 postmenopausal women with severe OP in 28 centres across 10 countries were randomised 1:1:1 to receive daily subcutaneous (SC) injections of 80 µg ABL (n=824), 20 µg TPTD (n=818), or placebo (n=821), for a duration of 18 months. New morphometric vertebral FFs (the primary efficacy endpoint of the ACTIVE study) occurred in 0.6% of ABL-treated patients, in 0.8% of TPTD-treated patients, and in 4.2% of placebo-treated patients, with a statistically significant difference being reached between each of the anabolic agents and placebo. ABL treatment also decreased the risk of non-vertebral FFs (secondary endpoint of the study) compared with placebo. ABL and TPTD were not compared in terms of FF risk reduction because the study would have required a much larger sample size to yield the statistical power necessary to detect any significant difference. ABL significantly improved bone mineral density (BMD) at the lumbar spine (LS), femoral neck (FN) and total hip (TH) compared with placebo from baseline to 18 months, with a treatment difference of 10.4%, 4%, and 4.3%, respectively. BMD increases in the ABL-treated group were greater than those in the TPTD group at TH and FN at

all timepoints (6, 12 and 18 months), and at LS at 6 and 12 months, but not at 18 months. Improvements in BMD with both ABL and TPTD were statistically greater than placebo at all sites and at all timepoints. There were more adverse events (AEs), although mild to moderate in severity, in the ABL group (9.9%) than in the TPTD (6.8%) or placebo (6.1%) groups. These were nausea (1.6%), dizziness (1.2%), headache (1.0%), and palpitations (0.9%). No differences in serious AEs were observed among the three treatment groups. However, hypercalcaemia was significantly less frequent in the ABL-treated arm (3.4%) compared with the TPTD-treated arm (6.4%) at all timepoints. The bone resorption marker serum cross-linked C-telopeptide of type I collagen (CTX) was significantly lower in the ABL- compared with the TPTD-treated arm. Thus, it was hypothesised that the more pronounced resorptive action of TPTD might be responsible for the increased risk of hypercalcaemia compared with ABL. On the contrary, the bone formation marker serum procollagen type I N-propeptide (P1NP) increased in a similar fashion in the two groups during the first month of treatment, but after 3 months it began to decrease in the ABL group even though it always remained 50% above baseline also at 18 months.

Overall, the ACTIVE study led to three main conclusions: 1) daily SC administrations of 80 μg ABL for 18 months significantly decreased the risk of new vertebral or non-vertebral FFs compared with placebo, 2) ABL treatment may enhance BMD, especially at the femur which is rich in cortical bone, compared with both placebo and TPTD, and 3) hypercalcaemia was significantly less frequent in the ABL-treated arm than both the TPTD- and the placebo-treated groups (3). As a result, ABL was approved in several countries, including the United States (April 2017) (4) and the European Union (December 2022) (5).

ABL is a 34–amino acid synthetic analogue of PTH-related protein (PTHrP) whose anabolic effect is achieved, similarly to TPTD, thanks to transient binding to PTH type 1 receptor (PTH1R), a G protein-coupled receptor. It was shown that structurally different PTH-like ligands may bind with higher affinity to specific conformations of the PTH1R, inducing signalling responses differing in duration. In particular, TPTD binds selectively to a G protein-independent conformation of PTHR1, called R^0, inducing more prolonged and greater calcaemic responses compared to that induced by ABL, which binds selectively to a G protein-dependent receptor conformation of PTH1R, called RG. Since it was suggested that more intermittent exposures to PTH analogues provide more pronounced anabolic effects on bone with more limited anti-resorptive action, it was postulated that ABL may be more favourable on bone metabolism due to the more transient signalling ascribable to the selective binding of ABL to the RG conformation of PTH1R, as compared with TPTD (6). Following these findings, the differences between TPTD and ABL were investigated at the histological level, and it was shown that while TPTD may stimulate endocortical bone remodelling resulting in increased porosity at the bone cortex (7), ABL did not show such effect in either animals or humans (8). A comparative study on oestrogen-depleted mice published in 2023 expanded the knowledge on this topic. The authors claimed that while TPTD and ABL had similar effects on long bone biomechanics and gave similar protection from trabecular bone loss at the vertebrae, ABL had a more pronounced anabolic effect than TPTD on cortical bone, resulting in increased BMD and cortical area at the femur. Furthermore, only ABL succeeded at preventing cortical marrow enlargement due to enhanced endosteal resorption related to estrogen depletion. Interestingly, although both TPTD and ABL bind to PTH1R, the analysis of bulk RNA-Seq from cortical bone osteocytes showed that despite inducing similar transcriptomic changes, certain signalling pathways involving genes with a role in bone remodelling and postmenopausal OP were upregulated (the JAK/STAT pathway) or downregulated (the IP3 pathway) specifically by ABL, possibly explaining the differences in cortical responses between the two PTH-like agents (9). Hopefully, more studies in the future will help fully uncover the effects of ABL at the molecular and histological level and thus unveil the real differences from TPTD.

The previous paragraph may arise the question on whether ABL may be more efficacious than TPTD at improving BMD in osteoporotic patients eligible for anabolic therapy. As mentioned earlier, the ACTIVE trial was not conclusive in this regard due to an insufficient sample size (3). In a more recent report published in 2021, Cosman *et al*. claimed that at present it is still not possible to clearly establish the superiority of any anabolic agent over the other two (10). Four multicentre randomised clinical trials (RCT) and 12 post-hoc analyses for a total of 2938 postmenopausal women were included in a meta-analysis published in 2023 to try to answer such question. The results showed that ABL was significantly more effective than TPTD at improving BMD at the FN and the TH at 24 weeks, with a high grade of evidence. Such findings were not confirmed at the LS, although this result was classified as with very low grade of evidence, probably due to the large heterogeneity in ABL dosages among the 16 studies involved in the analysis. Again, the occurrence of hypercalcaemia in the ABL-treated patients was half as common as in the TPTD-treated group, although without statistical significance (11), as opposed to what was observed in the ACTIVE trial (3). In conclusion, the superiority of either anabolic agent remains controversial, and more high-quality RCTs with large sample sizes are needed to better address this issue.

Because no Japanese patients were included in the ACTIVE and ACTIVExtend trials, a multicentre, double-blind phase 2 RCT involving ABL treatment was recently conducted at 10 sites in Japan (ACTIVE-J trial); 139 Japanese postmenopausal women with OP at high risk of FFs were randomised 1:1:1 to receive daily SC injections of 40 or 80 μg ABL or placebo for 48 weeks. The results published in 2023 were consistent with the global ACTIVE study and

showed that ABL treatment increased BMD at LS, at FN, and at TH in a dose-dependent manner, with 80 μg ABL being more effective than 40 μg, and with both being significantly more effective than placebo. Most AEs were mild or moderate and were not dose-dependent; the most common were, again, headache and dizziness. The small sample size and the short duration of the study did not allow to estimate the efficacy of ABL at reducing FF risk. In conclusion, ABL proved efficacious and safe also in Japanese postmenopausal women with OP (12). Consequently, a phase 3 RCT was conducted at 21 sites in Japan; both postmenopausal women and men with OP were randomised 2:1 to receive daily SC injections of 80 μg ABL or a placebo for 18 months. BMD at LS, FN and TH increased throughout ABL treatment, whereas only a small increase in LS BMD and almost no changes in TH and FN BMD values were observed in the placebo group, with a statistically significant difference between the two groups being reached already at 3 months. In the ACTIVE-J trial, treatment differences in BMD between the ABL and placebo groups were more pronounced at the LS, and were similar at TH and FN, compared with what was observed in the ACTIVE study. Even though AEs were more frequent in the ABL group (32%) than in the placebo group (13.9%), the most serious AEs occurred in the latter group. In conclusion, the efficacy of ABL in Japanese patients was comparable to that observed in the ACTIVE study (13). An exploratory analysis using the data from the ACTIVE-J trial evaluated the effects of ABL on hip geometry and biomechanical properties in Japanese men and postmenopausal women with OP by means of dual-energy x-ray absorptiometry (DXA)-based hip structural analysis (HSA). Bone geometric parameters and derived strength indices such as the periosteal outer diameter (OD), average cortical thickness (CoTh), bone cross-sectional area (CSA), cross-sectional moment of inertia (CSMI), section modulus (SM), and buckling ratio (BR) were calculated at the narrowest diameter of the FN (NN), at the intertrochanteric (IT) region along the bisector of the neck-shaft angle, and at the proximal femoral shaft (FS) 2 cm distal to the midpoint of the lesser trochanter. The results suggested that daily 80 μg ABL SC injections for 18 months versus placebo significantly and rapidly improved bone structural strength in all investigated regions, indicating the potential reduction in the risk of hip FFs in Japanese patients (14).

At present, all available anabolic therapies including PTH-like agents require SC injections for their administration. Despite their considerable benefit especially for individuals at high risk for FFs, many patients refuse daily SC injections thereby limiting the adherence to anabolic therapy (15). Even though several attempts have been made to produce alternative ways of administration for TPTD, none has eventually reached clinical practice (16). An alternative, short-weartime transdermal method of administration, called the solid microstructured transdermal system (sMTS), was recently developed for ABL and compared with the standard SC administration in a phase 3, open-label, multicentre, non-inferiority RCT, whose results were published in 2023. A total of 255 and 256 patients were randomised to receive 80 μg of ABL-SC and 300 μg of ABL-sMTS, respectively, for a 12-month period. Skin reactions at the administration site, mostly mild in intensity, were more common in the sMTS group, whose safety profile was otherwise comparable to the SC group. The least-squares mean percentage change from baseline in LS BMD at 12 months were 7.14% in the sMTS group and 10.86% in the SC group, with a treatment difference of -3.72%. Due to the failure to achieve a non-inferiority cut-off of at least -2%, the sMTS method did not prove non-inferior to the standard SC method of administration, although clinically relevant improvements in LS BMD were reached with both methods (17). Considering the global crisis related to OP treatment gap (18), reaching adequate compliance with therapy with AOMs among osteoporotic patients is fundamental. The development of new ways of administration alternative to SC injections for anabolic agents, including ABL, is a key step in the process.

Take home messages

- ABL is an anabolic AOM which can provide significant increases in BMD (3). Despite claims of more beneficial effects compared with TPTD especially at sites rich in cortical bone (9), high-quality comparative studies between ABL and TPTD with large sample sizes are needed.
- Hypercalcaemia was significantly less common in ABL- than in TPTD-treated patients (3).
- ABL proved safe and efficacious in recently published RCTs involving Japanese patients (12) (13).
- Transdermal ABL administration did not prove non-inferior to the standard subcutaneous injections (17). At present, there is no way of administration for anabolic agents other than subcutaneous injections.

Trabecular bone score (TBS) and estimation of fragility fracture risk: what's new?

As mentioned earlier, both bone mass, expressed as BMD, and bone microarchitecture, defined as the organisational properties of bone, may be at the basis of OP and the subsequent FF risk. It was previously shown that most FFs are not justified by BMD values in the osteoporotic range, *i.e.* T-scores below -2.5 on DXA scans (19). Therefore, it was suggested that, besides BMD measured by DXA, a comprehensive bone assessment should also include trabecular bone score (TBS), a grey-level texture measurement acquired by conventional DXA images at the spine level which can provide an estimation of the quality of bone microarchitecture (20). A review published in 2015 by an Expert Working Group of the European Society on Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) stated that TBS can predict major osteoporotic FFs at least partially independently of BMD and clinical risk factors (CRF), and suggested that TBS may potentially change during therapy with AOMs (21). New evidence supporting the role of TBS for FF risk estimation in both primary and secondary OP was gathered and discussed in a more recent paper pub-

lished in 2023 (22). Throughout this chapter, we provide a comprehensive analysis of its most relevant points.

Firstly, in consideration of the available and most recent literature, the authors provided recommendations with high level of evidence which stated 1. that TBS can predict FFs independently of BMD and CRFs present in the Fracture Risk Assessment Tool (FRAX®) algorithm; 2. that the combination of FRAX® and TBS has a greater value than FRAX® alone when predicting FF probability in postmenopausal women and men over the age of 50; and 3. that TBS adjustment is most useful in individuals with T-scores or FRAX[â] scores close to intervention thresholds to guide the appropriate management strategies (22).

The review (22) also focused on the effect on TBS by different AOMs. It was concluded that anti-resorptive treatment with BPs, SERMs, and MHT should be considered when the preservation rather than the increase in TBS is the goal of treatment. By contrast, long-term treatment with denosumab may result in significant TBS gains as shown in a recent international RCT, in which the proportion of postmenopausal women with degraded TBS and treated with denosumab decreased from 48.6% to 29.1%, and that with normal TBS increased from 26.1% to 53.2%; notably, greater improvements in TBS were also associated with a reduced incidence of FFs, thus further highlighting the role of TBS as a FF predictor (23).

The studies included in the review showed that all anabolic agents may lead to notable TBS improvement. A RCT involving postmenopausal women with glucocorticoid-induced OP showed significant TBS improvements with a mean of 3.7% at 36 months in the TPTD-treated group compared with the alendronate (ALN)-treated group, in which TBS did not change significantly at any timepoint (24). Cosman *et al*. recently carried out a post-hoc analysis (25) on 911 Caucasian women who completed the ACTIVE (3) and ACTIVExtend trials (26) and with available TBS corrected for soft tissue based on abdominal tissue thickness (TBS_{th}) at baseline, 6, 18, and 43 months, to assess whether mean TBS improved after 18 months of ABL treatment compared with placebo (ACTIVE trial), and to evaluate whether such improvement would stabilise during subsequent 2-year treatment with ALN (ACTIVExtend trial). The results showed a TBS_{th} increase from baseline by 2.4% at 6 months and 4% at 18 months in the ABL-treated group, with a statistically significant difference at both timepoints compared with the placebo group in which there was no significant change in TBS_{th}. The cumulative increase in TBS_{th} from baseline considering also the ACTIVExtend trial was 4.4% in the ABL/ALN group and 1.7% in the placebo/ALN group, with a statistically significant difference at 43 months. Finally, TBS_{th} increased from baseline to equal to or above least significant change (LSC) in 52% of the women who were treated with ABL/ALN, compared with 32% in the placebo/ALN group; a much lower probability of having a vertebral FF was seen in patients who reached TBS_{th} ≥LSC (25). For what concerns romosozumab, results from the Active-Controlled Fracture Study in Postmenopausal Women With Osteoporosis at High Risk (ARCH) RCT showed that TBS improved significantly with a mean of 5.1% compared to ALN, which did not achieve statistically significant changes in TBS, and that among women treated with romosozumab, those with degraded TBS decreased from 52.6% to 33% and those with normal TBS increased from 28.9% to 48.1% at the end of the study (27). These results led to the conclusion that TBS in combination with BMD is useful for monitoring the response to anabolic agents (22).

Another section of the review (22) focused on secondary OP, defined as OP caused or exacerbated by other diseases or by exposure to certain medications, primarily glucocorticoids (GC) and aromatase inhibitors (AI). The suspicion for secondary OP should arise especially when considering men and premenopausal women, although it is often found also in postmenopausal women (28). Shevroja et al. stated that degraded TBS may be observed in most diseases associated with secondary OP, and that TBS can predict FF risk independently of BMD in type 2 diabetes mellitus (T2DM), chronic kidney disease, GC-induced OP, and rheumatological diseases including both connective tissue diseases and inflammatory arthropathies. Furthermore, the skeletal effects of treatment with AI and GC have been shown to be reliably monitored by the combination of TBS and BMD. Despite limited evidence, TBS seems to be less affected by degenerative or inflammatory spinal changes, namely osteophytes and syndesmophytes, thereby possibly improving the estimation of FF risk in individuals with overestimated BMD values in the presence of a discordantly lower TBS. Nevertheless, it is still recommended to exclude vertebrae with structural abnormalities both from BMD and from TBS analysis (22).

Notably, the positive effect of anabolic treatment on TBS was proven also in the context of secondary OP. In a post-hoc analysis of the ACTIVE trial on 198 postmenopausal osteoporotic women affected by T2DM, which is known to be associated with decreased bone turnover, reduced serum PTH levels and serum markers of bone formation, it was observed that the 65 women treated with ABL for 18 months had significant TBS improvements with a mean percentage change from baseline of 3.72% at LS compared with placebo (-0.56%), and when comparing ABL and TPTD, TBS gains at LS were more rapid at 6 months (2.63% *vs*. -1.32%, respectively) and overall numerically more pronounced in the ABL group (3.72% *vs*. 2.37% at 18 months, respectively), although without reaching statistical significance at any timepoint (29).

Take home messages

- TBS is an independent predictor of FFs and enhances the predictive power of FRAX®, both in primary and secondary OP (22).
- TBS may have a decisive role in driving management of OP patients with T-scores on DXA or FRAX® scores close to intervention thresholds (22).

- Anti-resorptive agents, except for denosumab (23), provide preservation rather than enhancement of TBS. All anabolic agents proved efficacious in improving TBS (22).

Comparing anti-osteoporotic medications in terms of reduction of fragility fracture risk: what do we know?

FF prevention is the most important outcome in OP management; however, few RCTs have been carried out to compare the effect of different AOMs on FF risk (30). With the assumption that understanding such differences may improve the development of treatment guidelines, Händel *et al*. carried out a systematic review, network meta-analysis, and meta-regression analysis of 69 RCTs including more than 80,000 patients to characterise the effect of AOMs on FF risk according to baseline CRFs. The primary outcome was all clinical fractures excluding fingers and toes; the secondary outcomes were vertebral FFs, non-vertebral FFs, hip fractures, and major osteoporotic FFs, as defined in the RCTs. For clinical fractures and major osteoporotic FFs, the results highlighted that BPs, PTH analogues and romosozumab showed a protective effect compared with placebo, whereas denosumab and SERMs did not. BPs were less effective than PTH analogues, and denosumab was less effective than PTH analogues and romosozumab. For vertebral FFs, all AOMs were more effective than placebo, with denosumab, PTH analogues, and romosozumab being superior to oral BPs; at the hip, only SERMs had no protective effect for hip FFs. Network meta-analyses could not be performed for non-vertebral FFs. In the meta-regression analyses, anti-resorptive therapy provided a more pronounced incidence reduction of FFs with older patients, compared with placebo; conversely, baseline CRFs had no role in the effects of all other AOMs. In particular, anabolic agents proved more effective at reducing FFs than anti-resorptive drugs, with their comparative efficacy being independent of CRFs. Therefore, the authors concluded that 1. Anti-resorptive agents may be especially beneficial for the oldest patients to reduce their FF risk, and 2. OP management guidelines may allow an earlier introduction of anabolic agents, without restricting their administration only on patients with the highest risk of FFs (2).

Despite their advantage over anti-resorptive therapy in terms of FF risk reduction and BMD and TBS gains, another recent network meta-analysis found that ABL and TPTD gave a higher incidence of withdrawals due to AEs, the most of which were nausea, dizziness, vomiting, headache, palpitations, and leg cramps, compared with BPs. The authors also highlighted the relative gap in the literature concerning the risk of FFs seen in the context of sequential therapy with AOMs with different mechanisms of action (31). Nevertheless, considering that BMD reduction at the hip and radius and accelerated bone turnover were observed in women switching from denosumab to TPTD (32), it is generally not recommended to administer anabolic therapy after denosumab or BPs (31), especially BPs with longer skeletal half-lives which may partially impair the action of anabolic therapies administered afterwards, although apparently without negative influence on FF risk (33). Conversely, there is evidence that the use of oral BPs may efficiently maintain BMD gains obtained from initial therapy with TPTD (34) and ABL (26). Furthermore, denosumab after initial therapy with TPTD may enhance BMD and lead to a significantly lower incidence of FFs, without an increased occurrence of AEs (35). It was also observed that denosumab after romosozumab also sustained further BMD gains as compared with placebo, with which BMD values tended to diminish towards baseline levels; a decrease of bone turnover markers was also observed compared with placebo (36). In conclusion, the available evidence suggests that the best strategy for reducing FF risk consists of anabolic therapy to enhance TBS and BMD followed by anti-resorptive agents to maintain such enhancements. However, more data on FFs in the context of this type of sequential therapy is needed (37).

Take home messages

- Recent evidence suggested that anabolic treatment could not be restricted to patients with the highest FF risk, and may be beneficial also for patients with lower risk profiles (2).
- Sequential therapy should consist of anabolic agents for TBS and BMD enhancement followed by anti-resorptive treatment for TBS and BMD stabilisation, and not *vice versa* (31).

References

1. MAFFI M, DE MATTIA G, MAZZANTINI M: Osteoporosis and gut microbiota, radiofrequency echographic multispectrometry and machine learning: one year in review 2023. *Clin Exp Rheumatol* 2023; 41(7): 1377-83. https://doi.org/10.55563/clinexprheumatol/ma4l1t
2. HÄNDEL MN, CARDOSO I, VON BÜLOW C *et al*.: Fracture risk reduction and safety by osteoporosis treatment compared with placebo or active comparator in postmenopausal women: systematic review, network meta-analysis, and meta-regression analysis of randomised clinical trials. *BMJ* 2023; 381: e068033. https://doi.org/10.1136/bmj-2021-068033
3. MILLER PD, HATTERSLEY G, RIIS BJ *et al*. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. *JAMA* 2016; 316(7): 722-33. https://doi.org/10.1001/jama.2016.11136 Erratum in: *JAMA* 2017; 317(4): 442.
4. SHIRLEY M: Abaloparatide: first global approval. drugs. 2017; 77(12): 1363-68. https://doi.org/10.1007/s40265-017-0780-7
5. DAVENPORT C, GRAVEL P, WANG Y, WILLIAMS SA, WIELAND A, MITLAK B: Real-world evidence to support the registration of a new osteoporosis medicinal product in Europe. *Ther Innov Regul Sci* 2024; 58(3): 505-18. https://doi.org/10.1007/s43441-024-00616-7
6. HATTERSLEY G, DEAN T, CORBIN BA, BAHAR H, GARDELLA TJ: Binding selectivity of abaloparatide for PTH-Type-1-receptor conformations and effects on downstream signaling. endocrinology. 2016; 157(1): 141-49. https://doi.org/10.1210/en.2015-1726
7. LEDER BZ: Parathyroid hormone and parathyroid hormone-related protein analogs in osteoporosis therapy. *Curr Osteoporos Rep* 2017; 15(2): 110-19. https://doi.org/10.1007/s11914-017-0353-4
8. DEMPSTER DW, ZHOU H, RAO SD *et al*.: Early effects of abaloparatide on bone formation and resorption indices in postmenopausal women with osteoporosis. *J Bone Miner Res* 2021; 36(4): 644-53. https://doi.org/10.1002/jbmr.4243
9. LV Z, ZHANG J, LIANG S *et al*.: Comparative study in estrogen-depleted mice identifies skeletal and osteocyte transcriptomic responses to abaloparatide and teriparatide. *JCI Insight* 2023; 8(20): e161932. https://doi.org/10.1172/jci.insight.161932
10. COSMAN F, DEMPSTER DW: anabolic agents for postmenopausal osteoporosis: how do

you choose? *Curr Osteoporos Rep* 2021; 19(2): 189-205. https://doi.org/10.1007/s11914-021-00663-1
11. HONG P, LIU R, RAI S *et al*.: Is abaloparatide more efficacious on increasing bone mineral density than teriparatide for women with postmenopausal osteoporosis? An updated meta-analysis. *J Orthop Surg Res* 2023; 18(1): 116. https://doi.org/10.1186/s13018-023-03595-x
12. MATSUMOTO T, SONE T, YAMASHITA A, INOUE T: Abaloparatide dose-dependently increases bone mineral density in postmenopausal women with osteoporosis: a phase 2 study. *J Bone Miner Metab* 2023; 41(6): 807-16. https://doi.org/10.1007/s00774-023-01455-6
13. MATSUMOTO T, SONE T, SOEN S, TANAKA S, YAMASHITA A, INOUE T: Abaloparatide increases lumbar spine and hip BMD in Japanese patients with osteoporosis: the Phase 3 ACTIVE-J study. *J Clin Endocrinol Metab* 2022; 107(10): e4222-e4231. https://doi.org/10.1210/clinem/dgac486
14. SONE T, OHNARU K, SUGAI T *et al*.: The effects of abaloparatide on hip geometry and biomechanical properties in Japanese osteoporotic patients assessed using DXA-based hip structural analysis: results of the Japanese phase 3 ACTIVE-J trial. *Arch Osteoporos* 2023; 18(1): 146. https://doi.org/10.1007/s11657-023-01344-5
15. FRAENKEL L, GULANSKI B, WITTINK D: Patient treatment preferences for osteoporosis. *Arthritis Rheum* 2006; 55(5): 729-35. https://doi.org/10.1002/art.22229
16. SALAVE S, RANA D, PRAYAG K *et al*.: Recent advances in teriparatide delivery by-virtue-of novel drug delivery approaches for the management of osteoporosis. *Crit Rev Ther Drug Carrier Syst* 2023; 40(5): 93-123. https://doi.org/10.1615/critrevtherdrugcarriersyst.2023045014
17. LEWIECKI EM, CZERWINSKI E, RECKNOR C *et al*.: Efficacy and safety of transdermal abaloparatide in postmenopausal women with osteoporosis: a randomized study. *J Bone Miner Res* 2023; 38(10): 1404-14. https://doi.org/10.1002/jbmr.4877
18. KANIS JA, NORTON N, HARVEY NC *et al*.: SCOPE 2021: a new scorecard for osteoporosis in Europe. *Arch Osteoporos* 2021; 16(1): 82. https://doi.org/10.1007/s11657-020-00871-9
19. SANDERS KM, NICHOLSON GC, WATTS JJ *et al*.: Half the burden of fragility fractures in the community occur in women without osteoporosis. When is fracture prevention cost-effective? *Bone* 2006; 38(5): 694-700. https://doi.org/10.1016/j.bone.2005.06.004
20. CAREY JJ, BUEHRING B: Current imaging techniques in osteoporosis. *Clin Exp Rheumatol* 2018; 36 Suppl. 114(5): S115-26.
21. HARVEY NC, GLÜER CC, BINKLEY N *et al*.: Trabecular bone score (TBS) as a new complementary approach for osteoporosis evaluation in clinical practice. *Bone* 2015; 78: 216-24. https://doi.org/10.1016/j.bone.2015.05.016
22. SHEVROJA E, REGINSTER JY, LAMY O *et al*.: Update on the clinical use of trabecular bone score (TBS) in the management of osteoporosis: results of an expert group meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), and the International Osteoporosis Foundation (IOF) under the auspices of WHO Collaborating Center for Epidemiology of Musculoskeletal Health and Aging. *Osteoporos Int* 2023; 34(9): 1501-29. https://doi.org/10.1007/s00198-023-06817-4
23. HANS D, MCDERMOTT M, HUANG S, KIM M, SHEVROJA E, MCCLUNG M: Long-term effect of denosumab on bone microarchitecture as assessed by tissue thickness-adjusted trabecular bone score in postmenopausal women with osteoporosis: results from FREEDOM and its open-label extension. *Osteoporos Int* 2023; 34(6): 1075-84. https://doi.org/10.1007/s00198-023-06708-8
24. SAAG KG, AGNUSDEI D, HANS D *et al*.: Trabecular bone score in patients with chronic glucocorticoid therapy-induced osteoporosis treated with alendronate or teriparatide. *Arthritis Rheumatol* 2016; 68(9): 2122-28. https://doi.org/10.1002/art.39726
25. COSMAN F, HANS D, SHEVROJA E, WANG Y, MITLAK B: Effect of abaloparatide on bone microarchitecture assessed by trabecular bone score in women with osteoporosis: post hoc analysis of ACTIVE and ACTIVExtend. *J Bone Miner Res* 2023; 38(4): 464-70. https://doi.org/10.1002/jbmr.4764
26. BONE HG, COSMAN F, MILLER PD *et al*.: ACTIVExtend: 24 months of alendronate after 18 months of abaloparatide or placebo for postmenopausal osteoporosis. *J Clin Endocrinol Metab* 2018; 103(8): 2949-57. https://doi.org/10.1210/jc.2018-00163
27. MCCLUNG M, BETAH D, LEDER B *et al*.: Effect of romosozumab on bone microarchitecture as assessed by tissue thickness–adjusted trabecular bone score in postmenopausal women with osteopo- rosis: results from the ARCH study. https://eposters.asbmr.org/asbmr/2022/eposter/368700.
28. STEIN E, SHANE E: Secondary osteoporosis. *Endocrinol Metab Clin North Am* 2003; 32(1): 115-34, vii. https://doi.org/10.1016/s0889-8529(02)00062-2
29. DHALIWAL R, HANS D, HATTERSLEY G *et al*.: Abaloparatide in postmenopausal women with osteoporosis and type 2 diabetes: a post hoc analysis of the ACTIVE study. *JBMR Plus* 2020; 4(4): e10346. https://doi.org/10.1002/jbm4.10346 Erratum in: *JBMR Plus* 2020; 5(2): e10414.
30. SAAG KG, PETERSEN J, BRANDI ML *et al*.: Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med* 2017; 377(15): 1417-27. https://doi.org/10.1056/nejmoa1708322
31. AYERS C, KANSAGARA D, LAZUR B, FU R, KWON A, HARROD C: Effectiveness and safety of treatments to prevent fractures in people with low bone mass or primary osteoporosis: a living systematic review and network meta-analysis for the American College of Physicians. *Ann Intern Med* 2023; 176(2): 182-95. https://doi.org/10.7326/m22-0684 Erratum in: *Ann Intern Med* 2023; 176(6): 884.
32. LEDER BZ, TSAI JN, UIHLEIN AV *et al*.: Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. *Lancet* 2015; 386(9999): 1147-55. https://doi.org/10.1016/S0140-6736(15)61120-5
33. KENDLER DL, MARIN F, ZERBINI CAF *et al*.: Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet* 2018; 391(10117): 230-40. https://doi.org/10.1016/S0140-6736(17)32137-2 Erratum in *Lancet* 2018; 391(10117): 204; Erratum in *Lancet* 2018; 392(10162): 2352.
34. NIIMI R, KONO T, NISHIHARA A, HASEGAWA M, KONO T, SUDO A: Efficacy of switching from teriparatide to bisphosphonate or denosumab: a prospective, randomized, open-label trial. *JBMR Plus* 2018; 2(5): 289-94. https://doi.org/10.1002/jbm4.10054
35. LIU Y, XU Y, ZHANG X, LI J, XIA Y, CHU H: Evaluating the clinical efficacy of teriparatide and denosumab combination therapy in postmenopausal osteoporosis: a systematic review and meta-analysis. *Altern Ther Health Med* 2023 Nov 10: AT9688.
36. MCCLUNG MR, BROWN JP, DIEZ-PEREZ A *et al*.: Effects of 24 months of treatment with romosozumab followed by 12 months of denosumab or placebo in postmenopausal women with low bone mineral density: a randomized, double-blind, phase 2, parallel group study. *J Bone Miner Res* 2018; 33(8): 1397-406. https://doi.org/10.1002/jbmr.3452
37. CHANDRAN M: The why and how of sequential and combination therapy in osteoporosis. A review of the current evidence. *Arch Endocrinol Metab* 2022; 66(5): 724-38. https://doi.org/10.20945/2359-3997000000564