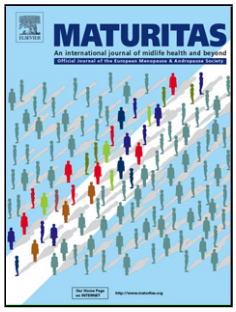

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Authors: Panagiotis Anagnostis, Nifon K. Gkekas, Michael Potoupnis, Eustathios Kenanidis, Eleftherios Tsiridis, Dimitrios G. Goulis

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Review

New therapeutic targets for osteoporosis

Panagiotis Anagnostis[1,2,3], Nifon K. Gkekas[2,3], Michael Potoupnis[2,3], Eustathios Kenanidis[2,3], Eleftherios Tsiridis[2,3], Dimitrios G. Goulis[1,2]

[1]Unit of Reproductive Endocrinology, First Department of Obstetrics and Gynecology, Medical School, Aristotle University of Thessaloniki, Greece

[2]Centre of Orthopaedic and Regenerative Medicine Research (CORE), Center for Interdisciplinary Research and Innovation (CIRI), Aristotle University of Thessaloniki, Thessaloniki, Greece

[3]Academic Orthopaedic Unit, Aristotle University Medical School, General Hospital Papageorgiou, Thessaloniki, Greece

Corresponding author: Panagiotis Anagnostis, MD, PhD, MSc, FRSPH, Unit of Reproductive Endocrinology, First Department of Obstetrics and Gynaecology, Medical School, Aristotle University of Thessaloniki, "Papageorgiou" General Hospital, 56403, NeaEfkarpia, Thessaloniki, Greece, phone: 0030 2310 257150, fax: 0030 2310 281179, e-mail: anagnwstis.pan@yahoo.gr.

Highlights

- Abaloparatide, a PTH-related peptide (PTHrP) synthetic analogue, leads to greater gain in bone mineral density compared with teriparatide, and therefore to a lower risk of major fractures and hypercalcaemia.
- Romosozumab, a sclerostin inhibitor, is associated with greater reductions in the risk of vertebral, non-vertebral and hip fractures compared with either placebo or alendronate, but potentially with a higher cardiovascular risk.

- Anabolic therapy should always be followed by administration of an anti-resorptive agent, with denosumab providing the greatest benefit, especially after its prior combination with teriparatide.

Abstract

New anti-osteoporotic agents have been developed, potentially enriching the therapeutic armamentarium. Currently available osteoanabolic therapies are the parathyroid hormone (PTH) and PTH-related peptide (PTHrP) synthetic analogues, teriparatide and abaloparatide. Daily administration at doses of 20 and 80 μg, respectively, in contrast to continuous PTH secretion, leads to increased bone formation and reduces vertebral and non-vertebral fracture risk. Teriparatide is more effective than bisphosphonates (alendronate, risedronate) in increasing bone mineral density (BMD), improving bone architecture and reducing fracture risk. Abaloparatide leads to greater BMD gain, has greater anti-fracture efficacy regarding major osteoporotic fractures (upper arm, wrist, hip or clinical spine) compared with teriparatide (without a difference in morphometric vertebral and non-vertebral fractures), and has a lower risk of hypercalcaemia. Romosozumab, a sclerostin inhibitor, both induces bone formation and suppresses bone resorption. Administered as monthly subcutaneous doses of 210 mg, it reduces vertebral, non-vertebral and hip fracture risk compared with either placebo or alendronate. However, concerns have arisen about increased cardiovascular risk, which has suspended its approval by the FDA. Anabolic therapy should always be followed by administration of an anti-resorptive agent, such as bisphosphonates or denosumab, which preserves and may further increase BMD gain. Denosumab provides the greatest benefit for BMD when administered sequentially after its combination with teriparatide for 24 months and constitutes a reasonable option for patients at high risk of fracture. However, longitudinal data are needed to confirm the efficacy and safety of these therapeutic interventions.

Keywords: osteoporosis, anabolic therapy, teriparatide, abaloparatide, romosozumab

1. Introduction

Osteoporosis is a chronic disease affecting millions of people worldwide, characterised by a deterioration of bone microarchitecture, predisposing to increased risk of fracture, which affects the quality of life and increases mortality in both sexes [1, 2]. Initial management usually includes an anti-resorptive agent with anti-fracture efficacy, such as selective oestrogen receptor modulators (SERMs) (raloxifene, bazedoxifene), oestrogen replacement therapy (when vasomotor symptoms co-exist and affect quality of life), bisphosphonates and denosumab. Anabolic therapy may also be used in patients with high fracture risk, usually as a second-line treatment [teriparatide, a parathyroid hormone (PTH) synthetic analogue, as well as abaloparatide, a PTH-related peptide (PTHrP) synthetic analogue] [3]. Nevertheless, most patients will need more than one anti-osteoporotic agent during their lifetime [3]. Despite the well-documented efficacy of the above therapies, unmet needs for a more effective anti-fracture strategy still exist. From this perspective, the better understanding of biological pathways of bone metabolism and osteoblastic differentiation, such as the Wnt pathway, has led to the advent of new compounds that induce bone formation and, what is of utmost importance, without coupling or even suppressing bone resorption.

The main aim of this narrative review is to present the current evidence on the efficacy of the new anabolic anti-osteoporotic agents and to compare these with established, therapies. An additional aim is to review the evidence on combined and sequential treatment with older and novel compounds.

2. Methods

The PubMed database was searched for English language publications, from inception until 15th October 2018, using the following terms: ("anabolic therapy"OR "parathyroid hormone" OR "PTH(1-84) OR "teriparatide" OR "abaloparatide" OR "sclerostin inhibitors" OR "romosozumab") AND ("osteoporosis" OR "fracture(s)" OR "sequential therapy" OR "combination therapy" OR "drug holidays"). Additionally, the reference sections of the reviewed articles were used to widen the search. The review collected, analysed and qualitatively re-synthesised information regarding: (i) the effectiveness of the newly anabolic anti-osteoporotic therapies, (ii) their comparison with teriparatide or anti-resorptive agents with regard to their effect on BMD and anti-fracture efficacy and (iii) current evidence on the combined and sequential treatment with anti-osteoporotic medications.

3. Bone anabolic therapies

The two currently available anabolic therapies are teriparatide and abaloparatide. These are synthetic analogues of PTH and PTHrP, respectively. PTH is an 84-amino acid polypeptide that binds to PTH/PTHrP type 1 receptor (PTH1R). It increases renal calcium reabsorption at the proximal tubule, osteoclastic activity and intestinal calcium absorption (indirectly, through activation of the 1α-hydroxylase enzyme in the kidneys, which transforms the 25-hydroxyvitamin D to its active form, the 1,25-dihydroxyvitamin D) [4]. PTHrP is a 34-amino acid polypeptide, which also binds to the PTH1R. It also increases bone resorption and renal tubular calcium reabsorption, without playing any role in intestinal calcium absorption [5]. It is widely expressed in many tissues during skeletal development. PTHrP has been shown to modulate chondrocyte differentiation and osteoblast function, mammary gland formation, calcium transport through the placenta, vascular smooth muscle differentiation, tooth development and pancreatic β-cell proliferation[5]. Experimental studies have shown that

selective deletion of the PTHrP gene leads to decreased bone formation and low bone mass. PTHrP loss of function has also been associated with skeletal deformities in humans, such as in Blomstrand's chondrodysplasia [5].

3.1. Teriparatide

Teriparatide shares the first active 34 amino acids of the N-terminal end of the PTH molecule and can increase bone formation when administered intermittently, in contrast to the continuous effect of PTH in primary hyperparathyroidism. Teriparatide also binds to the PTHR. It is administered subcutaneously at a daily dose of 20 μg, for a total of 24 months. The proposed underlying mechanisms for teriparatide's anabolic effect, although not fully elucidated, include Wnt 10b signalling stimulation, sclerostin inhibition, increased insulin-like growth factor-1 and osteocalcin production [6, 7].

Teriparatide has proven efficacy in reducing vertebral and non-vertebral fracture risk in postmenopausal women with osteoporosis [8], as well as in patients with glucocorticoid-induced osteoporosis, showing greater anti-fracture efficacy in the latter situation, when compared with alendronate [9]. Teriparatide is also indicated in male osteoporosis, as it increases BMD, an effect that is maintained 30 months after its discontinuation [10]. There is also evidence regarding vertebral fracture risk reduction in these patients [10] as well as for greater resolution of osseous defects of the oral cavity compared with placebo [11], a promising effect in cases of jaw osteonecrosis [12]. Furthermore, in a recent comparative study, teriparatide was more effective in reducing vertebral and clinical fracture risk when compared with weekly risedronate, after 24 months of therapy (no difference in non-vertebral fracture risk) [13].

3.2. Abaloparatide

Abaloparatide shares the same 1-22 amino acid sequence with PTHrP, but differs in amino acids 23-34. It has a higher affinity for the RG and a lower affinity for the R0 conformation of the PTH1R compared with teriparatide, exerting a more potent osteoanabolic effect [14]. It induces bone formation, avoiding the coupling with bone resorption [15]. Data from animal and human studies demonstrate that abaloparatide increases significantly both cortical thickness and trabecular bone [16-18].

In the hallmark clinical study, the Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE), abaloparatide (n=824; 80 μg/d) was compared with teriparatide (n=818; 20 μg/d) or placebo (n=821) for 24 months, in postmenopausal women at high risk of fracture (mean age 69 years)[19]. Abaloparatide reduced the risk of new morphometric vertebral fractures [0.6% versus 4.2%; relative risk (RR) 0.14; 95% confidence interval (CI) 0.05 to 0.39] and non-vertebral fractures [2.7% versus 4.7%; hazard ratio (HR) 0.57; 95% CI 0.32 to 1.00] over 18 months compared with placebo. No difference with teriparatide was observed in morphometric vertebral fractures. However, the risk reduction for major osteoporotic fractures of the upper arm, wrist, hip or clinical spine was greater with abaloparatide compared with both placebo or teriparatide [1.5% for the abaloparatide group versus 6.2% for the placebo group (HR 0.30; 95% CI, 0.15 to 0.61) versus 3.1% for the teriparatide group (HR 0.45; 95% CI 0.21 to 0.95)]. Moreover, the increase in BMD at 12 months with abaloparatide was significantly greater than placebo in lumbar spine (LS), total hip (TH) and femoral neck (FN) (mean changes from baseline: +9.77%, +3.41% and +2.65% versus +0.45%, +0.09%, -0.41%, respectively, $p<0.01$). These changes were also greater compared with teriparatide at 12 months, but not in LS at 18 months (+11.2% and +10.3%, respectively) [19]. This differential effect on BMD by PTH and PTHrP analogues has also been shown in earlier phase II studies [20]. Abaloparatide was generally well-tolerated with a

very low risk of adverse events, which included nausea (1.6%), dizziness (1.2%) and headaches (1%). Of note, the incidence of hypercalcaemia was significantly lower with abaloparatide compared with teriparatide (3.4% versus 6.4%, respectively) [19].

The calculated number needed to treat (NNT) for abaloparatide, by using reference populations from historical placebo-controlled trials, for vertebral, non-vertebral, clinical and significant osteoporotic fractures were 28, 55, 37 and 34, respectively. The respective NNT for teriparatide in the ACTIVE study were 30, 92, 59, and 75 [21]. *Post-hoc* analysis of the same study has shown a beneficial effect of abaloparatide (n=51) compared with placebo (n=43) in women aged ≥80 years with increases in BMD of 12.1%, 3.6% and 3.9% at the LS, FN and TH, similar to those observed in the overall population. However, the reduction in fracture risk was not significant compared with placebo, in this subpopulation [22].

As with teriparatide, the abaloparatide administration should be followed by an anti-resorptive agent to maintain the gain in BMD [23]. In this concept, an extension of the ACTIVE, the "ACTIVExtend" study, was conducted, during which alendronate was administered for 24 months after the initial 18-month treatment period with abaloparatide (n=558) or placebo (n=581) [24]. At the end of a 43-month period, an 84% RR reduction (RRR) for new radiographic vertebral fractures was found for the alendronate/abaloparatide group compared with the alendronate/placebo group [24]. A similar RRR (87%) was observed for the 24-month period. The BMD gains achieved during the ACTIVE study were maintained and further increased in the former group [24].

Following the results from the ACTIVE and ACTIVExtend trials, abaloparatide received approval by the US Food and Drug Administration (FDA) in 2017, for patients with osteoporosis at high fracture risk, defined as a history of osteoporotic fracture or multiple risk

factors for fracture, as well as for patients not responding or intolerant to other osteoporosis therapies [25]. Interestingly, when compared with teriparatide, abaloparatide proved to be more cost-effective, when both drugs are followed by an anti-resorptive agent, such as alendronate [26]. Treatment duration of both teriparatide and abaloparatide is limited to 24 months, based on the results of the above trials, which were terminated due to the theoretical risk of osteosarcoma, seen in rodent models, which has not been replicated in human studies [27].

3.3 Romosozumab

Since the discovery of the Wnt signalling pathway, one of the determinants of osteoblastic differentiation, a more "anabolic-based" approach has been developed for osteoporosis treatment. Major extracellular inhibitors of this pathway are sclerostin and Dickkopf-1 (Dkk-1), which are secreted by the osteocytes and bind to lipoprotein receptor related-proteins 4, 5 and 6 (LRP4, LRP5, LRP6, respectively). These substances eventually suppress osteoblastic activity, differentiation, and survival [28]. Sclerostin-inhibition also suppresses osteoclastic activity, since sclerostin upregulates synthesis of the receptor activator of nuclear factor-kB (RANK) ligand (RANKL), which is the primary determinant of osteoclastic differentiation, thereby stimulating bone resorption [28].

Romosozumab is a humanised monoclonal antibody against sclerostin. Human and animal studies support an increase in bone formation combined with a decrease in bone resorption. This dual action leads to changes in bone architecture, by rapidly increasing both trabecular and cortical bone mass, as well as whole bone stiffness [29]. In its first hallmark clinical study, the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME), patients with FN or TH T-scores of -2.5 to -3.5, were randomly assigned to monthly subcutaneous

doses of romosozumab 210 mg (n=3,321, mean age 70.8 years) or placebo (n=3,322, mean age 70.9 years) for 12 months. After that, both groups received two doses of denosumab (60 mg, every six months) and fracture incidence was assessed at 24 months. Romosozumab was associated with a 73% and 75% RRR of vertebral fractures at 12 and 24 months, respectively (RR 0.27, 95% CI 0.16 to 0.47, HR 0.75, 95% CI 0.57 to 0.97), respectively]. Romosozumab also led to a 36% RRR in clinical fractures (HR 0.64,95% CI 0.46 to 0.89), although no difference in non-vertebral fracture incidence was noticed between the two groups [30]. A comparative study showed that BMD gain at two years (after the initial 12-month administration) was similar to the one achieved by denosumab alone after seven years of continuous use, as seen in the Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM) and its extension studies [31].

In the other hallmark study, the Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH), 4,093 women (mean age 74 years) with osteoporosis and a fragility fracture were assigned to either romosozumab (210 mg) or weekly alendronate (70 mg) for 12 months and followed by open-label alendronate for additional 12 months. Over a total of 24 months, romosozumab/alendronate reduced vertebral, non-vertebral, hip and clinical fracture risk by 48% (RR 0.52, 95% CI 0.40 to 0.66), 19% (HR 0.81, 95% CI 0.66 to 0.99), 38% (HR 0.62, 95% CI 0.42 to 0.92) and 27% (HR 0.73, 95% CI 0.61 to 0.88), respectively [32]. Furthermore, patients randomised to romosozumab/alendronate achieved higher BMD values at all skeletal sites than with alendronate alone [32]. It must be emphasised that discontinuation of romosozumab was followed by bone loss and the return of BMD to pre-treatment levels, whereas sequential administration of denosumab further increased BMD, after two years of romosozumab therapy [33].

Romosozumab has also proven efficacy in male osteoporosis, by significantly increasing BMD in LS (+12.1% versus +1.2%), TH (+2.5% versus -0.5%) and FN (+2.2% versus -0.2%) compared with placebo, already from the six months. As in the previous studies, a significant increase in bone formation and a decrease in bone resorption markers was observed with romosozumab. Although the study was not powered to show anti-fracture efficacy, a lower rate of fractures (1.8%) was noticed in the romosozumab group than in the placebo group (2.5%) [34].

Notwithstanding its anti-fracture efficacy, a higher risk in severe adjudicated cardiovascular disease (CVD) events where observed in the ARCH study with romosozumab compared with alendronate (2.5% versus 1.9%), yielding an odds ratio (OR) of 1.31 (95% CI 0.85 to 2.00), attributed mainly to ischemic heart disease (OR 2.65, 95% CI 1.03 to 6.77) and cerebrovascular disease (OR 2.27, 95% CI 0.93 to 5.22). However, rates of heart failure, non-coronary revascularisation and peripheral vascular disease not requiring revascularisation were numerically lower in the romosozumab group [32]. This increased risk was also observed in the BRIDGE study [34].

The exact pathogenetic mechanisms for such an association of romosozumab with high cardiovascular risk have not been clarified. These may reside in the inhibitory role of sclerostin on vascular calcification [35], although this has not been verified in experimental animal studies [36]. A potential cardioprotective role of alendronate should also be taken into account [37]. No increase in CVD risk was observed in the FRAME study [30]. These concerns have suspended romosozumab approval by the FDA. Another adverse effect, except

for injection site reactions, is the development of anti-romosozumab antibodies in 13-18% of cases, which do not compromise its effectiveness [30, 32].

4. Sequential therapy

In general, the optimal therapeutic strategy after discontinuation of an osteo-anabolic therapy has not been established. According to an older consensus, switching to a more potent therapy may be considered in cases of: (i) ≥2 incident fragility fractures, (ii) one incident fracture and increased concentrations of bone turnover markers or a significant decrease in BMD or both, (iii) both no significant decrease in bone turnover markers and a significant decrease in BMD [38]. Three general rules may be followed in these cases: (i) a weaker anti-resorptive may be replaced by a more potent drug of the same class, (ii) an oral medication may be substituted by an intravenous one, and (iii) a strong anti-resorptive is replaceable by an anabolic agent [38]. Since then, new data have emerged recently and are presented below.

4.1. Anti-resorptive after osteo-anabolic therapy

BMD gain may be lost after cessation of anabolic therapy. For this purpose, sequential therapy with anti-resorptive agents has been tested. Alendronate was one of the first agents used in this strategy, after completion of PTH(1-84) therapy, leading to a further increase in BMD, especially in the trabecular bone [39, 40]. Raloxifene has also been used for this purpose, showing a beneficial effect after one year of teriparatide in maintaining LS BMD and increasing hip BMD[41]. The ACTIVExtend study was the first to test the efficacy of the sequential administration of an anti-resorptive agent (alendronate) after completion of the specified therapy of an anabolic compound, with the fracture incidence constituting the primary endpoint. Abaloparatide followed by alendronate regimen was more effective in

fracture risk reduction compared with placebo followed by alendronate. Thus, there is no evidence for the anti-fracture efficacy of this sequential therapeutic strategy, except for BMD maintenance [24].

4.2. Osteo-anabolic after anti-resorptive therapy

By contrast, prior use of bisphosphonates, especially those of longer skeletal half-lives, seems to blunt the expected BMD increase with teriparatide [42], although this has not been confirmed in all studies [43]. Romosozumab has also been tested in women previously treated with bisphosphonates for at least three years (n=218), in a head-to-head comparison with teriparatide (n=218). After 12 months, romosozumab induced greater BMD changes at all skeletal sites compared with teriparatide (+9.8% versus +5.4% in LS, +2.9% versus +0.5% in TH and +2.9% versus -0.5% in FN, respectively) [44]. In structural analysis, romosozumab resulted in greater increases in cortical, but no difference in trabecular bone scores, compared with teriparatide [44].

4.3. Combination therapy

A more effective therapeutic approach is still needed that offers simultaneous inhibition of bone resorption and induction of bone formation. In this regard, denosumab administered after teriparatide seems not only to preserve, but also to further increase BMD. The DATA-Switch study was an extension of the initial Denosumab and Teriparatide Administration (DATA) study [45], which demonstrated a preponderance of the combination of teriparatide and denosumab over either treatment alone. Women initially assigned to teriparatide received denosumab (n=28), those assigned to denosumab were switched to teriparatide (n=31), and those who received the combination therapy were assigned to additional 24 months of denosumab (n=28) [46]. After a total of 48 months, the increase in LS BMD was 18.3%, 14%, and 16%, respectively, without difference between groups. Regarding TH, BMD

increased in both teriparatide and combination groups who switched to denosumab (+6.6% and +8.6%, respectively), whereas transition from denosumab to teriparatide resulted in a decrease in BMD (+2.8% from baseline, -0.7% from 24 to 48 months). Similar changes were observed in FN and distal radius, with the most significant effect observed with the "denosumab after combination" group (+9.1% and +2.8%, respectively) [46].

Further analysis with high-resolution peripheral quantitative computerised tomography (HR-pQCT) showed a significant gain in cortical thickness and estimated strength with denosumab alone after combination with teriparatide compared with any of the other regimens (notably, a decrease with teriparatide followed by denosumab was observed) [47]. Older studies showed similar LS, but greater hip BMD increases with PTH(1-84) combined with alendronate than either treatment alone [48], whereas teriparatide alone was more effective than its combination with alendronate [49]. On the other hand, zoledronic acid combined with teriparatide was equally effective with zoledronic acid monotherapy in hip BMD and with teriparatide monotherapy in LS BMD [50].

In conclusion, alendronate seems to be a reasonable and practical option after PTH analogues and abaloparatide, as well as raloxifene, although to a lesser extent. Romosozumab is more effective than teriparatide, after prior therapy with bisphosphonates, whose action may blunt the expected BMD gain with teriparatide. However, these results cannot be applied in daily clinical practice, due to its current suspension by the FDA. Denosumab, especially after its 24-month combination with teriparatide, exerts the most potent effect on BMD.

4.4. Anti-resorptive following another anti-resorptive therapy

In general, it is not clear when to discontinue anti-osteoporotic medications, except for the defined duration of osteo-anabolic therapies. Due to the risk (albeit relatively low) of adverse events with bisphosphonate use, such as jaw osteonecrosis and atypical femoral fractures, and its long-term affinity to the skeleton, the concept of a "drug holiday" has been developed. According to the international societies' guidelines, such as those released by the European Menopause and Andropause Society (EMAS), current data are available only for alendronate, risedronate, and zoledronic acid. Alendronate and zoledronic acid may be discontinued after five and three years of continuous use, respectively, provided that the patient not be at high risk (defined as a T-score at the hip of <-2.5 or incidence of a new fragility fracture during treatment). In this regard, risedronate may be withdrawn for no more than one year after at least three years of continuous use [51]. Regarding denosumab, the optimal treatment duration is a matter of debate. A recent extension of the FREEDOM study has established its long-term safety and efficacy for a continuous BMD increase at all skeletal sites without a plateau, and further fracture risk reduction [52]. Following denosumab discontinuation, BMD rapidly declines and bone turnover markers are increasingly high. Therefore, close monitoring and administration of an anti-resorptive agent are recommended to reduce the risk of a rebound fracture, as this has been the subject of numerous case reports [51].

In general, data are still inconclusive concerning the efficacy of sequential therapy with bisphosphonates after denosumab. In one study (n=50), after four years of denosumab plus teriparatide treatment (in three different combinations), anti-resorptive therapy, including denosumab (n=10), oral bisphosphonates (n=10) and intravenous zoledronic acid (n=8), prevented bone loss, in comparison with placebo [23]. Contradictory data exist regarding zoledronic acid use after denosumab, although from small sample sizes. In one study (n=6), a single zoledronic acidinjection after seven years of denosumab administration retained LS but

not hip BMD above pre-denosumab levels after 18-23 months of follow-up [53]. Another study (n=22) showed a protective effect against rebound fractures with a single dose of zoledronic acid immediately after five denosumab injections, over 24 months of follow-up, despite the loss of one-third of the gain in BMD with denosumab [54]. Others (n=11) reported higher BMD retention (73% at the LS and 87% at the TH) 12 months after one single infusion [14]. Lower retention rates (41-64%) have been reported with risedronate [55], whereas alendronate may be more effective in BMD stabilisation after denosumab discontinuation [56]. Although it is believed that exposure to bisphosphonates before denosumab may prevent further bone loss, this does not seem to eliminate the risk of spontaneous vertebral fractures [57].

5. Conclusions

A new era has emerged in osteoporosis treatment, characterised by a more anabolic-oriented approach. Both the PTHrP synthetic analogue abaloparatide and the sclerostin-inhibitor romosozumab, by stimulating bone formation (the former without coupling with, the latter with simultaneous suppression of bone resorption), appear effective in increasing BMD in all skeletal sites and reduce vertebral and non-vertebral fracture risk. However, an association of romosozumab with increased cardiovascular risk has suspended its FDA approval. Anabolic therapy should always be followed by administration of an anti-resorptive agent, such as bisphosphonates or denosumab, the latter having a greater effect. Combination of teriparatide with denosumab followed by denosumab is currently the most potent therapeutic approach, which may be beneficial in patients with very low bone mass, unresponsive to other therapies. Long-term treatment with denosumab must also be followed by an anti-resorptive agent, such as alendronate, to preserve BMD gain. Whether these strategies are also translated into fracture risk reduction remains to be established.

Contributors

Panagiotis Anagnostis designed the study, searched the literature, analyzed the data and wrote the first draft of the paper.

Nifon K. Gkekas was responsible for the data synthesis, the text format and reviewed the manuscript.

Michael Potoupnis reviewed the manuscript and provided critical scientific input.

Eustathios Kenanidis reviewed the manuscript and provided critical scientific input.

Eleftherios Tsiridis reviewed the manuscript and provided critical scientific input.

Dimitrios G. Goulis resolved discrepancies regarding the quality of the studies, provided critical scientific input and had the primary responsibility for the paper's final content.

Conflict of interest

The authors have no conflict of interest to declare.

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