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Advances in the Treatment of Bone-Forming Drugs Contribute to Osteoporosis Diseases

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Abstract

Osteoporosis is a chronic disease in the elderly. At present, more anti-osteogenesis drugs (bisphosphonates, estrogen receptor modulators, calcitonin, etc.) are used in clinical treatment in China. However, with the advent of osteogenic drugs represented by parathyroid hormone (PTH), it has brought new choices for clinical treatment of osteoporosis, but there are not many reports on the use of domestic osteogenic drugs. In the treatment of international osteoporosis, some new target therapeutic drugs have been developed to enrich treatment. Currently available bone anabolic therapies for osteogenic drugs are mainly parathyroid hormone and parathyroid hormone synthetic analogues (PTHrP) such as teriparatide and apalaparatide. Studies have shown that in the experimental group administered daily at doses of 20 and 80 micrograms, the osteogenesis of the experimental group increased and the risk of vertebral and non-vertebral fractures decreased compared with the blank group with only continuous PTH secretion. Teriparatide is more effective than bisphosphonates (Alendronate, Risedronate) in increasing bone density, improving bone structure and reducing fracture risk. Compared with teriparatide, the increase in bone mineral density of abaloparatide is more pronounced and has a significant effect on osteoporotic fractures (upper arm, wrist, hip or clinical spine) and have a lower risk of hypercalcemia. Romosozumab is a sclerostin inhibitor that induces both bone formation and bone resorption, reducing the risk of vertebral, non-vertebral and hip fractures.

Keywords

Osteoporosis Drugs, Tripapeptide, Appalapaatin, Romosozumab, Osteoporosis

成骨药物对骨质疏松疾病促成骨代谢治疗的研究进展

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摘　要

骨质疏松是一种老年慢性疾病。当前国内临床治疗使用较多的是抗骨吸收药物(双膦酸盐、雌激素受体调节剂、降钙素等)。但随着甲状旁腺素(parathyroid hormone, PTH)为代表的成骨药物的出现，为临床治疗骨质疏松带来新的选择，但国内成骨药物的使用报道还并不多。在国际的骨质疏松疾病的治疗中，目前已经开发了一些新的靶点治疗药物来丰富治疗手段。目前可用的骨合成代谢疗法的成骨药物主要是甲状旁腺激素和甲状旁腺激素合成类似物(PTHrP)如特立帕肽(teriparatide)和阿巴拉帕肽(abaloparatide)。有研究证明每日给药剂量为20和80微克的实验组，与只有连续的PTH分泌的空白组相比，实验组的成骨增加，并且椎体和非椎体骨折的风险降低。在增加骨密度、改善骨结构和降低骨折风险方面，特立帕肽(Teriparatide)比双膦酸盐(阿仑膦酸盐(Alendronate)，利索膦酸钠(Risedronate)更有效。与特立帕肽(Teriparatide)相比，阿巴拉帕肽(Abaloparatide)骨密度的增加作用更加显著，对骨质疏松性的骨折(上臂、手腕、髋部或临床脊柱)具有很显著的效果，并有较低的高钙血症风险。罗莫索珠单抗(Romosozumab)是一种硬化蛋白抑制剂，既能诱导骨形成，又能抑制骨吸收，它能减少椎体，非椎体和髋部骨折的风险。

关键词

促成骨代谢药物，特立帕肽，阿巴拉帕肽，罗莫索珠单抗，骨质疏松

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1. 引言

骨质疏松症是一种影响全世界数百万人的慢性疾病，其特征是骨微结构的恶化，增加骨折风险，影响患者生活质量并增加死亡率[1] [2]。初始治疗通常包括具有抗骨折功效的抗骨吸收药物，如选择性雌激素受体调节剂(SERMs) (雷洛昔芬(raloxifene)，巴多昔芬(Bazedoxifene)，雌激素替代品治疗(双膦酸盐)。促成骨代谢药物疗法也可用于高骨折风险的患者，通常作为二线治疗(特立帕肽－甲状旁腺激素(PTH)合成类似物，以及阿巴拉帕肽-PTH (PTHrP)合成类似物)。然而，大多数患者在其一生中需要一种以上的抗骨质疏松剂[3]。尽管上述疗法的功效已得到充分证实，但仍需要更有效的抗骨折治疗方案。随着基础研究更充分地了解骨代谢和成骨细胞分化的生物学途径，例如 Wnt 途径，科学家们已经开发出了新的治疗药物。在本文中总结了新合成抗骨质疏松药物功效的现有证据，并将这些提出的治疗方法进行比较，同时也归纳了旧药的和新药的联合的研究证据。

促成骨代谢疗法目前可用的两种合成代谢疗法是特立帕肽和阿巴拉帕肽。它们分别是甲状旁腺激素和甲状旁腺激素合成类似物。PTH 是 84 个氨基酸的多肽，其与 PTH/PTHrP-1 型受体(PTH1R)结合。它增加肾小管近端小管的重吸收，破骨细胞活性和肠钙吸收(通过间接激活肾脏中的 1α-羟化酶，将 25-羟基维生素 D 活化为 1,25-二羟基维生素 D) [4]。PTHrP 是 34 个氨基酸的多肽，骨骼发育期在许多组织中广泛

表达。与 PTH1R 结合后，增加骨吸收和肾小管钙重吸收，但不会对肠道钙吸收起任何作用[5]。PTHrP 已被证明可调节软骨细胞分化和成骨细胞功能，乳腺形成，同时通过胎盘的钙转运影响血管平滑肌分化，牙齿发育和胰腺 β 细胞增殖[5]。实验研究表明，PTHrP 基因的选择性缺失会导致骨形成减少和骨量减少。PTHrP 功能丧失也与人类的骨骼畸形有关，例如 Blomstrand 的软骨发育不良[5]。

2. 特立帕肽(Teriparatide)

特立帕肽与 PTH 分子的 N’端有 34 个相同的氨基酸，当间歇给药时可以增加骨形成。特立帕肽也与 PTHR 结合。该研究实验中以 20 μg 的日剂量皮下给药，总共 24 个月。文末提出的特立帕肽合成代谢作用的潜在机制，虽然尚未完全阐明，但可能和 Wnt10b 信号刺激，硬化蛋白抑制，增加的胰岛素样生长因子-1 和骨钙素的产生等有关[6] [7]。特立帕肽已被证实可有效降低绝经后骨质疏松症患者的椎骨和非椎体骨折风险[8]，以及糖皮质激素诱导的骨质疏松症患者，与阿仑膦酸盐相比，它具有更强的抗骨折疗效[9]。特立帕肽也适用于男性骨质疏松症，因为它会增加骨密度，这种效应在停药后 30 个月仍然存在[10]。还有证据表明，与安慰剂组相比，这些患者的脊椎骨折风险降低[10]以及改善了牙齿和颌骨的钙质丢失[11]，这在颌骨坏死的情况下具有良好的效果[12]。此外，在最近的比较中研究表明，与治疗 24 个月后的每周利塞膦酸盐相比，特立帕肽在降低椎体和临床骨折风险方面更有效(非椎体骨折风险无差异)[13]。

3. 阿巴拉帕肽(Abaloparatide)

阿巴拉帕肽与 PTHrP 具有相同的 1~22 个氨基酸序列，但在 23~34 号位序列中的氨基酸不同。与特立帕肽相比，它对 RG 具有更高的亲和力，对 PTH1R 的 R0 构象具有更低的亲和力，发挥更强效的骨代谢作用[14]。它诱导骨形成，避免骨吸收[15]。来自动物实验和人体研究的数据表明，阿巴拉帕肽能显著增加皮质厚度和骨小梁[16] [17] [18]。在标志性临床研究中，将阿巴拉帕肽比较试验在脊椎终点(ACTIVE)，阿巴拉帕肽(n = 824; 80 μg/d)与特立帕肽(n = 818; 20 μg/d)还有安慰剂组(n = 821)进行了为期 24 个月的比较[19]。阿巴拉帕肽降低了椎体骨折的风险[0.6%对 4.2%；相对风险(RR) 0.14；]和非椎骨骨折[2.7%对 4.7%；风险比(HR) 0.57；]。在椎骨骨折中没有观察到和特立帕肽的差异，然而，与安慰剂组或特立帕肽相比，阿巴拉帕肽在上臂，腕关节，髋关节或临床脊柱位主的骨质疏松性骨折的风险降低更多[阿巴拉帕肽组为 1.5%，而安慰剂组为 6.2%，而特立帕肽组为 3.1%]。此外，在腰椎(LS)，全髋(TH)和股骨颈(FN)中，阿巴拉帕肽在 12 个月时的骨密度增加显著高于安慰剂(从基线的平均变化：+9.77%，+3.41%和+2.65%对比+0.45%，+0.09%，−0.41%，$p < 0.01$) [19]。II 期研究[20]也显示 PTH 和 PTHrP 类似物对 BMD 的不同影响. 阿巴拉帕肽一般耐受性良好，不良事件风险极低，包括恶心(1.6%)，头晕(1.2%)和头痛(1%)。值得注意的是，与特立帕肽相比，阿巴拉帕肽的高钙血症发生率显著降低(分别为 3.4%和 6.4%) [19]。在这个概念中，进行了 ACTIVE 的“ACTIVExtend”研究的延伸，其中阿仑膦酸盐在最初的 18 个月治疗期后用阿巴拉帕肽(n = 558)或安慰剂(n = 581)给药 24 个月。在 43 个月结束时，阿仑膦酸盐/阿巴拉帕肽组与阿仑膦酸盐/安慰剂组相比，新发现的放射性椎体骨折的 RR 降低了 84%。在 ACTIVE 研究期间实现的骨密度增加在前一组中得以维持并进一步增加[21] [22] [23] [24]。根据 ACTIVE 和 ACTIVExtend 试验的结果，阿巴拉帕肽于 2017 年获得美国食品和药物管理局(FDA)的批准，用于骨折风险高的骨折患者，为有骨质疏松性骨折史或多种骨折危险因素以及对其他骨质疏松症治疗无反应或不耐受的患者[25]。有趣的是，与特立帕肽相比，阿巴拉帕肽被证明更具成本效益[26]。根据上述试验的结果，特立帕肽和阿巴拉帕肽的治疗持续时间限制为 24 个月，由于在啮齿动物模型中观察到的骨肉瘤的理论风险而终止，这在人类研究中尚未复制[27]。

4. 罗莫索珠单抗(Romosozumab)

罗莫索珠单抗是一种抗硬化蛋白的人源化单克隆抗体。自从发现 Wnt 信号通路(成骨细胞分化的决定因素)以来，已经开发了一种更加“基于合成代谢”的方法用于骨质疏松症治疗。该途径的主要细胞外抑制剂是硬化蛋白和 Dkk-1 (Dickkopf-1 由骨细胞分泌并结合脂蛋白受体蛋白 LRP4，LRP5，LRP6)。这些物质最终抑制成骨细胞活性，并影响其分化和存活[28]。硬化蛋白抑制也抑制破骨细胞活性从而刺激骨吸收[28]。人和动物研究支持骨形成的增加以及骨吸收的减少。这种双重作用通过快速增加骨小梁和皮质骨影响整个骨骼硬度导致骨骼结构的变化[29]。在其第一个临床研究中发现，绝经后骨质疏松症女性骨折研究，FN 或 THT 评分为−2.5 至−3.5 的患者被随机分配为每月皮下注射罗莫索珠单抗 210 mg (n = 3321，平均年龄 70.8 岁)或安慰剂(n = 3322，平均年龄 70.9 岁)，为期 12 个月。之后，两组均接受两剂 denosumab (60 mg，每 6 个月一次)，并在 24 个月时评估骨折发生率。 罗莫索珠单抗分别在 12 个月和 24 个月时存在 73%和 75%的椎体骨折。罗莫索珠单抗组临床骨折的存活率为 36%，但两组患者的非椎体骨折发生率无差异[30]。一项对比研究显示，连续使用 7 年后，两年内(最初 12 个月给药后)的骨密度增加与单独使用 Denosumab 所获得的相似[31]。在另一项研究中，高风险骨质疏松症(ARCH)的绝经后妇女的研究，将 4093 名患有骨质疏松症和脆性骨折的女性(平均年龄 74 岁)分配到罗莫索珠单抗(210 mg)或每周阿仑阿仑膦酸钠(70 毫克) 12 个月，然后开放标记阿仑膦酸盐再加 12 个月。罗莫索珠单抗/阿仑膦酸钠在 24 个月内使椎骨，非椎骨，髋部和临床骨折风险降低 48%，38%和 27% [32]。此外，随机分配到罗莫索珠单抗/阿仑膦酸钠的患者在所有骨骼部位的骨密度值均高于单用阿仑膦酸钠[32]。但必须强调的是，停用罗莫索珠单抗后骨质流失和骨密度恢复到了治疗前水平，而经过两年的罗莫索珠单抗治疗后，连续给予 denosumab 可进一步增加骨密度[33]。与安慰剂组相比，罗莫索珠单抗在男性骨质疏松症中的疗效显著增加，显著增加 LS 的骨密度(+12.1%对比+1.2%)，TH (+2.5%对−0.5%)和 FN (+2.2%对比−0.2%)，$P < 0.05$。虽然该研究无法显示抗骨折疗效，但罗莫索珠单抗组的骨折率(1.8%)低于安慰剂组(2.5%) [34]。尽管具有抗骨折功效，但在 ARCH 研究中使用罗莫索珠单抗与阿仑膦酸钠(2.5%对 1.9%)观察到严重心血管疾病(CVD)事件的风险较高，产生的比值比(OR)为 1.31 (95%)，主要归因于缺血性心脏病(OR 2.65)和脑血管疾病(OR 2.27)。然而，罗莫索珠单抗组的心力衰竭，非冠状动脉血运重建和不需要血运重建的外周血管疾病的发生率较低[32]。在 BRIDGE 研究中也观察到这种增加的风险[34]。罗莫索珠单抗与高血压相关的致病机制以及增加的心血管风险原因机制尚未明确。可能和硬化蛋白对血管钙化的抑制作用有关[35]，尽管这在动物实验研究中尚未得到证实[36]。还应考虑阿仑膦酸钠的潜在心脏保护作用[37]。在 FRAME 研究中没有观察到 CVD 风险的增加[30]。这些担忧也最使 FDA 暂停了对罗莫索珠单抗的批准。

5. 小结

骨质疏松症治疗出现了一个新时代，促骨形成药物与抗骨吸收药物的作用机制不同。PTH 为代表的促骨形成药物使用后，继续用抗骨吸收药可显著升高骨密度并降低骨折风险。PTHrP 合成类似物阿巴拉帕肽和硬化蛋白抑制剂罗莫索珠单抗，通过刺激骨形成有效增加所有骨骼部位的骨密度并减少椎骨和非脊椎骨折风险。另一方面，如在 PTH 治疗前使用双膦酸盐，PTH 仍然会起效，但可能会降低 PTH 的成骨效果。对于之前未接受过治疗的患者，直接采用 PTH 与阿仑膦酸钠联合治疗方案似乎没有优势。但可以考虑的联合治疗包括特立帕肽与 Denosumab 或者唑来膦酸联合。这些联合治疗可能有助于扩大 PTH 的“合成代谢窗”[38]。然而，罗莫索珠单抗与心血管风险增加的关联 FDA 已经暂停其批准。合成代谢治疗之后应始终给予抗再吸收剂，如双膦酸盐或 denosumab，后者具有更大的作用。特立帕肽与 denosumab 联合使用是目前最有效的治疗方法，这对于骨量非常低，对其他疗法无反应的患者可能是有益的。用

denosumab 长期治疗之后还必须使用抗再吸收剂，如阿仑膦酸盐，以保持骨密度增加。但是这些治疗方案是否也对骨折风险降低仍有待确定。上述联合治疗的安全性均可以接受，但考虑到缺少骨折发生率的数据，结果尚需在大样本人群中进一步研究。

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