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特立帕肽序贯治疗进展：基于中国国情的个体化治疗

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摘　要

中国65岁以上女性中近一半人患有骨质疏松。特立帕肽能够促进骨形成并改善骨微结构，从而提高骨密度，降低骨质疏松性骨折风险。然而，其促骨形成作用在停药后会迅速减弱，因此及时的序贯治疗非常重要。目前常用的序贯方案包括特立帕肽序贯阿仑膦酸、唑来膦酸及地舒单抗等，临床治疗中具体序贯药物需根据患者情况选择。在中国，特立帕肽价格较为昂贵，再加上使用方式相对不便，以致许多患者难以长期坚持用药。因此，个体化的序贯时机及药物选择尤为关键。对于经济条件有限或依从性较差的患者，在获得特立帕肽的促骨形成效益后，或许可以根据具体情况选择合适的抗骨吸收药物，适时实施早期序贯治疗。虽然目前已有相关临床研究，但还需要大样本的临床研究去验证此方案。这样不仅能够减轻患者的经济负担，还可提升骨质疏松症长期治疗的依从性和有效性。

关键词

特立帕肽，序贯治疗，骨质疏松症，个体化治疗

Advances in Sequential Therapy with Teriparatide: Toward Individualized Treatment in the Context of China

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Abstract

Nearly half of women aged 65 years and older in China are affected by osteoporosis. Teriparatide promotes bone formation and improves bone microarchitecture, thereby increasing bone mineral density and reducing the risk of osteoporotic fractures. However, its anabolic effect diminishes rapidly after discontinuation, making timely sequential therapy essential. Common sequential regimens include teriparatide followed by alendronate, zoledronic acid, or denosumab, with the choice of subsequent therapy determined by individual patient characteristics. In China, the high cost of teriparatide and its inconvenient mode of administration make long-term adherence challenging for many patients. Therefore, individualized timing and selection of sequential therapy are particularly important. For patients with limited financial resources or poor adherence, an appropriate antiresorptive agent may be selected after achieving the anabolic benefits of teriparatide, with early sequential therapy implemented as appropriate based on individual circumstances. Although relevant clinical studies are available, large-scale clinical trials are still needed to validate this approach. Such a strategy may not only reduce the economic burden on patients but also improve adherence and the long-term effectiveness of osteoporosis treatment.

Keywords

Teriparatide, Sequential Therapy, Osteoporosis, Individualized Treatment

1. 引言

骨质疏松症是一种以骨量减低、骨微结构损坏为特征，导致骨脆性增加和易发生骨折的全身性骨病[1]，是我国乃至全球面临的重大公共健康挑战[2] [3]。骨质疏松会导致骨折风险增加，骨质疏松性骨折致残率高，极大地威胁患者生命安全(如髋部骨折一年内死亡率可高达 20%)，给社会带来沉重的经济负担[4] [5]。特立帕肽(Teriparatide)是治疗骨质疏松的常用药物，是目前我国抗骨质疏松药物中，唯一正式用于临床的骨形成促进剂[1]，可显著促进成骨细胞活性，有效提升骨密度(Bone Mineral Density, BMD)，降低椎体和非椎体骨折风险[6]。

特立帕肽在停药后，其促骨形成作用会快速消退，若无序贯治疗，增加的骨密度将快速流失[7]。因此，多国骨质疏松指南均建议特立帕肽停药后需要序贯抗骨吸收药物继续治疗，当前最常见的序贯药物主要包括阿仑膦酸、唑来膦酸、地舒单抗等[1] [8]-[10]。

特立帕肽治疗骨质疏松性骨折中国专家共识(2024 版)推荐特立帕肽用于骨质疏松性骨折的初始治疗，以快速提升骨密度，降低再次骨折风险[11]。但在我国的具体国情下，特立帕肽的使用面临着特殊挑战。昂贵的价格加上相对不方便的使用方式(每日皮下注射)，严重影响了患者的可及性、依从性和持续性，许多患者难以完成推荐疗程，导致骨质疏松治疗效果不佳[12]-[14]。因此，合适的序贯时机和药物至关重要。探寻符合中国国情的个体化序贯策略，提升患者用药依从性，特别是为经济条件有限、依从性欠佳的患者，探索早期序贯治疗的可行性与时机，对我国骨质疏松患者的长期规范化治疗管理，具有极其重要的现实意义。

本文旨在系统综述特立帕肽序贯治疗的最新研究进展，重点围绕不同序贯方案的疗效与安全性比较、

序贯时机的选择及其影响因素展开讨论，并结合中国患者的临床特点与诊疗现状，探讨个体化序贯治疗策略的制定，以期为临床医生优化骨质疏松症的长程管理提供见解与参考。

2. 特立帕肽的作用机制及序贯治疗的理论基础

特立帕肽是一种重组人甲状旁腺激素(PTH)的活性片段(1~34)，与成骨细胞表面的PTH1受体(PTH1R)结合[15]，激活cAMP/PKA和PLC/PKC等多条信号通路，直接刺激成骨细胞增殖、分化并抑制其凋亡，延长其生命周期，从而促进骨形成[16] [17]。同时，特立帕肽还通过降低硬骨抑素(Sclerostin)表达，提高RANKL/OPG比值并促进破骨生成，对骨吸收起到一定的调控作用[18] [19]。其总体呈促骨形成效应，进而增加骨量，改善骨小梁微结构，提高骨骼的生物力学强度。但停药后特立帕肽对成骨细胞的刺激作用将会迅速消失，骨形成速率随之降低，而骨吸收相对亢进，导致骨转换“负平衡”[20]，即骨吸收大于骨形成，导致特立帕肽治疗获得的骨密度增益迅速丢失[21]。

抗骨吸收药物可抑制破骨细胞活性[22]，在特立帕肽停药后，及时序贯抗骨吸收药物，可将骨转换率稳定在较低水平，防止过度吸收特立帕肽期形成的骨基质[23]，给予已形成骨基质持续“二次矿化”时间，巩固特立帕肽带来的骨微结构改善[24]。

3. 特立帕肽的序贯方案

3.1. 特立帕肽序贯双膦酸盐药物

双膦酸盐类药物是治疗骨质疏松的一线药物，包括阿仑膦酸、唑来膦酸、利塞膦酸、伊班膦酸、米诺膦酸等[25]。目前，国内外指南均指出特立帕肽治疗结束后，可以选择序贯双膦酸盐类药物，从而维持或持续提升患者骨密度，降低骨折风险[8] [9]。虽然双膦酸盐类药物在临床使用非常广泛，但存在颌骨坏死(Osteonecrosis of the Jaw, ONJ)的风险，对于近期有口腔或牙科手术计划的患者，应在用药时予以充分警惕和评估[26]。

3.1.1. 特立帕肽序贯阿仑膦酸

阿仑膦酸可以增加骨质疏松患者的骨密度，降低椎体及非椎体的骨折风险[27]。研究显示，绝经后骨质疏松女性在接受1年PTH (1-84)治疗后继续序贯1年阿仑膦酸(10 mg/天，口服)，与无序贯治疗相比，在腰椎和全髋骨密度可获得进一步增加(4.9%和3.6%) [28]。此外，一项前瞻性研究[29]指出，相同疗程下，与单独使用阿仑膦酸钠相比，使用特立帕肽六个月后序贯阿仑膦酸钠治疗，也能带来持续的腰椎骨密度改善效果，且新发骨折率低于阿仑膦酸组(6.5% vs 23.7%)。

3.1.2. 特立帕肽序贯唑来膦酸

唑来膦酸可提高骨密度，降低椎体、髋部及其他部位的骨折风险[30]。唑来膦酸因其1年1次及静脉滴注的使用方式，在依从性方面优于其他口服类双膦酸盐药物。一项回顾性研究[31]显示，重度骨质疏松患者接受特立帕肽治疗24个月后，然后序贯24个月唑来膦酸治疗，其腰椎及髋部骨密度可分别增加22 ± 27%和17 ± 18%。

3.1.3. 特立帕肽序贯其他双膦酸盐类药物

常用的治疗骨质疏松的双膦酸盐类药物还包括伊班膦酸[32]、利塞膦酸[33]、米诺膦酸[34]等，均可以提升骨密度，降低骨折风险。其中米诺膦酸主要是在日本运用较为广泛。目前关于特立帕肽序贯这些药物的研究较少，大多数指南并未明确提及特立帕肽可以序贯这些药物。因此，还需要更严谨、更多的研究去证实序贯这些药物的科学性及临床可行性。

3.2. 特立帕肽序贯地舒单抗

地舒单抗是一种抗 RANK 配体单克隆抗体，能增加骨矿物质密度并降低骨折风险[35]。Leder 等的一项随机对照试验表明，绝经后骨质疏松的患者先接受特立帕肽治疗 24 个月，再转为地舒单抗治疗 24 个月，可使腰椎骨密度平均增加 18.3% [36]。Dito 等的研究也得到了相似的结果[31]。虽然进口的地舒单抗价格昂贵，但是地舒单抗的生物类似药(LY06006)解决了这个问题[37]。在中国，地舒单抗已经成为使用十分广泛的抗骨松药物，其受肝肾功能影响较小，且使用便捷(每半年皮下注射一次)，为提高患者依从性提供了优势。需要特别注意的是，地舒单抗停药后骨密度会迅速下降，需序贯使用其他抗骨吸收药来避免这种“反弹效应”[38]。

3.3. 特立帕肽序贯雷洛昔芬

雷洛昔芬是一种选择性雌激素受体调节剂(SERM) [39]，可增加绝经后骨质疏松症女性的脊柱和股骨颈骨密度，同时降低其椎体骨折风险[40]。一项纳入 380 名绝经后骨质疏松症患者的随机对照试验表明，1 年特立帕肽后序贯 1 年雷洛昔芬治疗，可显著提升股骨颈骨密度，并减轻腰椎骨质流失[41]。但在临床应用中，需警惕高血栓风险等情况。

4. 特立帕肽序贯的时机

目前多个国家的指南均指出，特立帕肽停药后应立即予以抗骨吸收药物进行序贯治疗，从而维持骨密度[1] [8]-[10]。

特立帕肽的最长使用疗程在我国不超过 2 年。一项 DATA-Switch 研究指出，特立帕肽使用 24 月后序贯地舒单抗治疗 24 个月，序贯治疗后腰椎、股骨颈、全髋骨密度分别继续增加 8.6%、5.6%、4.7% [36]。Cosman 等的前瞻性研究使用特立帕肽 18 个月后序贯地舒单抗 18 个月，序贯治疗后腰椎、股骨颈和全髋的骨密度均可继续增加，3 年后骨密度较基线分别增加 16%、3%和 4% [42]。有研究使用甲状旁腺激素(1-84) 12 个月后，序贯阿仑膦酸 12 个月，可以维持或继续增加骨密度，脊柱骨密度可增加 31% [28]。此外，有前瞻性研究[29]纳入 215 名完成经皮椎体成形术的骨质疏松症女性患者，使用特立帕肽 6 个月后，PINP 和 CTX 均明显升高，然后序贯阿仑膦酸治疗 6 个月，腰椎和股骨颈骨密度较序贯治疗前仍持续增加，这提示即使在早期(6 个月)序贯阿仑膦酸也可获得骨密度持续增加。

尽管序贯治疗的必要性已被广泛认同，但关于最佳序贯药物选择(如双膦酸盐与地舒单抗的优劣比较)、最佳序贯时机(早期序贯与完成疗程后序贯的疗效差异)等关键问题，仍缺乏明确的共识与指南推荐，需要最新的证据进行系统梳理与比较。应根据患者具体情况，如用药依从性、满意度、经济水平、受教育程度、基础疾病等方面综合考虑，选择准确的时机和合适的药物。

5. 我国具体情况与特立帕肽的用药管理

我国骨质疏松患者数量庞大。根据第七次全国人口普查数据，65 岁及以上人群已超过 1.9 亿，其中约 32%患有骨质疏松，女性患病率高达 51.6%。有研究预测[43]，到 2025 年我国可能有 599 万例骨质疏松相关骨折，造成约 254.3 亿美元的经济损失。我国骨质疏松患者在诊治率和药物治疗率上偏低，只有 6.5%的人在骨质疏松性骨折后 6 个月内接受了抗骨质疏松症药物治疗[2]。目前美国《AACE/ACE 绝经后骨质疏松症诊断和治疗指南-2020 更新》、我国《原发性骨质疏松症诊疗指南(2022)》等骨质疏松领域各大权威指南，均推荐特立帕肽为极高骨折风险患者的一线治疗药物。我国《特立帕肽治疗骨质疏松性骨折中国专家共识(2024 版)》指出，极高骨折风险患者，初始治疗推荐应用特立帕肽治疗(强推荐)。证实了特立帕肽在骨质疏松治疗中的地位。

依从性是影响骨质疏松治疗效果的关键因素，在考虑任何骨质疏松的治疗方案时，患者依从性都是重要的挑战[44]。研究表明，对特立帕肽治疗依从性高的患者，骨折风险更低[45] [46]。临床实践中，部分患者可能因费用、不良反应及给药方式等因素出现依从性差或提前停药的情况。完成特立帕肽疗程并及时序贯抗吸收药物的患者，可获得更好的骨密度增益及更低椎体骨折风险[46]。然而，由于特立帕肽需每日皮下注射，且价格昂贵、医保覆盖范围有限，其依从性普遍偏低。另有研究显示，不足一半的患者在停用特立帕肽后序贯抗骨吸收类药物[47]。因此，如何提升患者的用药依从性，提高序贯治疗率，是优化骨质疏松治疗效果的重要环节。

荷兰一项真实世界研究显示，在实施包含教育与激励的支持计划后，患者接受特立帕肽治疗的两年坚持率显著提高，提示系统化的依从性干预能够改善持续用药情况，从而最大化骨质疏松治疗获益[48]。此外，密切的电话随访同样被证实可提升患者对特立帕肽的依从性[49]。因此，在特立帕肽的长期用药管理中，应通过定期随访并加强用药教育与激励，以改善患者的依从性和持久性，从而进一步提高骨质疏松的治疗效果。

我国一项关于地舒单抗与特立帕肽治疗骨质疏松的经济学研究显示，地舒单抗的治疗成本明显低于特立帕肽(51224.64 元 vs. 167102.67 元)，具有显著的经济优势[50]。另一项采用马尔可夫模型进行成本效益分析进一步表明，与特立帕肽相比，地舒单抗在所有年龄段均具成本效益[51]。相比双膦酸盐类药物，特立帕肽同样未表现出经济学优势[52]。目前特立帕肽尚未被纳入《国家基本医疗保险、工伤保险和生育保险药品目录(2024 年)》[53] [54]，大部分患者仍需自费使用。在我国，许多患者因经济能力有限，且受教育程度较低，难以长期坚持使用特立帕肽进行治疗。

有研究提示[28] [29]，即使短时间使用特立帕肽治疗，较早序贯抗骨吸收类药物，也可获得临床骨密度获益。因此，临床上应根据患者的具体情况制定个体化的骨质疏松治疗方案。对于依从性差或经济条件不足的患者，在使用特立帕肽获得骨形成效益后，或许可以进行早期序贯治疗。这样不仅能够提高患者的依从性，减轻经济负担，还能在有限条件下实现更优的骨质疏松治疗效果。

6. 总结

特立帕肽作为目前临床治疗骨质疏松的重要药物之一，其具有促骨形成的作用，可明显提高患者骨密度，降低骨折风险，并被推荐用于骨质疏松伴极高骨折风险的人群。然而，其每日皮下注射方式和价格昂贵限制了临床的应用，使得患者的依从性和持久性不足，从而严重地影响患者的疗效。目前我国骨质疏松患者众多，探索更加经济有效、可操作性强的治疗模式尤为重要。未来临床实践中，对于依从性差或经济能力有限的患者，在特立帕肽发挥足够的促骨形成效益并且保证患者疗效的前提下，若患者难以继续使用特立帕肽，或许可考虑早期选择合适的药物进行序贯治疗。这将有助于提升患者依从性，降低经济负担，提高治疗效果。但是目前的研究数据有限，有待更多的、更大的临床研究去证实这种序贯时机的可行性及安全性，例如：特立帕肽早期序贯治疗(3 个月、6 个月)与一线抗骨吸收药物治疗的长期骨折率和成本效益的RCT研究，另外，特立帕肽在我国详细用药依从性的大样本真实世界研究是缺乏的，有待进一步研究。探索个体化的治疗模式，不仅符合我国国情，也有助于实现骨质疏松治疗的长期获益，值得在未来研究和临床应用中加以验证和优化。

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