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地舒单抗在骨质疏松中的应用研究进展

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摘　要

在全球老龄化背景下，骨质疏松成为了一个公众健康问题。骨质疏松是一种骨稳态失衡的全身性骨疾病，地舒单抗作为首个核因子κB受体活化因子配体(receptor activator nuclear of factor kappa-B ligand, RANKL)抑制剂应用于骨质疏松治疗取得不错的疗效。虽然在中国2020年上市，但国外已有10余年的临床应用经验和大量的相关研究，可预见其在中国的应用也会越来越广泛。现将地舒单抗在骨质疏松中的应用及研究进展予以综述。

关键词

地舒单抗，骨质疏松，核因子κB受体

Research Progress on the Application of Deshumazumab in Osteoporosis

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Abstract

In the context of global aging, osteoporosis has become a public health problem. Osteoporosis is a systemic bone disease with bone homeostasis imbalance. As the first inhibitor of nuclear factor kappa B receptor activating factor ligand, deschumab has achieved good results in the treatment of osteoporosis. Although it is listed in China in 2020, it has more than 10 years of clinical application

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experience and a large number of related researches abroad, and it can be predicted that it will be more and more widely used in China. In this paper, the application and research progress of desuximab in osteoporosis are reviewed.

Keywords

Deschumab, Osteoporosis, Nuclear Factor Kappa B Receptor

1. 引言

骨质疏松(osteoporosis, OP)是以骨矿物质密度(bone mineral density, BMD)下降和骨微结构破坏导致骨稳态失衡为特征的全身性骨疾病，尤其是绝经后女性在 50~59 岁年龄段之间的骨质疏松患病率能达到 1/5 [1]。骨稳态主要通过成骨细胞(osteoblast, OB)和破骨细胞(osteoclast, OC)之间动态平衡来维系。

骨强度降低及骨微结构破坏，使骨质疏松性骨折(osteoporotic fracture, OPF)风险升高[2]。人们将骨质疏松称为“沉默病”，患者多因难以忍受的疼痛或骨折后来院就医检查发现患有骨质疏松。同时临床医生对治疗前骨质疏松的评估意识还有待提高[3]，只有 1/10 的外科医生在术前行骨密度测量[4]。据统计，全球有 2 亿男性和女性患有 OP，60 岁以上人群 OP 合并骨折的风险大大增加[5]。OP 患者存在基数大、发病率高但知晓率低的窘况，在全球老龄化的背景下，OP 合并骨折更加重社会经济负担[6]。因此对 OP 发病机制的研究及相关治疗药物的研究成为众多医师关注的重点。地舒单抗(Denosumab)是 Amgen 公司研发的单克隆抗体(IgG2 型)，为全球首个 RANKL 靶向抑制剂，与核因子 κB 受体活化因子(receptor activator of nuclear factor-κB, RANK)竞争性结合 RANKL 抑制 OC 分化进而提高骨密度[7]。该药于 2010 年经美国食品药品监督管理局(Food and Drug Administration, FDA)批准上市用于骨质疏松治疗，但 2020 年才应用于我国，目前临床医师对该药的使用经验较少[8]。本文综述骨质疏松的病因机制及地舒单抗在骨质疏松治疗领域的相关研究进展，以期为地舒单抗的临床应用提供参考。

2. 骨质疏松

2.1. 骨质疏松的诊断

根据早期国际临床密度测定学会(The International Society for Clinical Densitometry, ISCD)对骨质疏松症定义：基于双能 X 线吸收检测法(dual energy X-ray absorptiometry, DXA)测量的 BMD (腰椎 1-4、腕部、股骨颈或全髋)，T 值 ≤−2.5 为骨质疏松[9]。其测定方法及数值标准沿用至今(表 1)。

Table 1. Diagnostic criteria of osteoporosis based on DXA bone mineral density T value
表 1. 基于 DXA 骨密度 T 值骨质疏松症诊断标准

分类	T 值
正常	T 值 ≥−1.0SD
骨量减小	−2.5SD < T 值 <−1.0SD
骨质疏松	T 值 ≤−2.5SD
严重骨质疏松	T 值 ≤−2.5 SD 合并脆性骨折

2.2. 骨质疏松病因

2.2.1. 激素影响

机体一定程度雌激素水平对骨骼具有保护作用，绝经后女性雌激素撤退，患骨质疏松的风险更高，在生活质量量表中，其风险较未绝经女性高处 5 倍[10]。Mohamad NV 等[11]发现雌激素在 OPG/RANKL/RANK 轴中扮演重要角色，雌激素减少可影响骨稳态平衡，延长 OC 的作用时间，促进骨吸收使骨量减低。Soysa NS 等[12]研究发现雌二醇(E2)可诱发 OC 凋亡，认为雌激素抑制 OC 的骨吸收保护骨组织。Bonaccorsi G 等[13]发现氧化应激作为绝经后骨质疏松症的致病性辅助因子证据充分，通过老鼠切除卵巢造成雌激素缺失影响免疫细胞(T、B)的合成，使炎症因子(IL-1、IL-6、TNFα 等)升高造成骨破坏。Almeida M 等[14]认为雄激素可作用于 OB 来保护男性松质骨，也可通过芳香化转为雌激素发挥骨保护作用。Urquiaga M 等[15]发现糖皮质激素使用者即使在非全身性给药途径和低剂量的情况下，导致腰椎、髋部的低 BMD，骨折风险高于非使用者。糖皮质激素通过增加 OC 活性和降低 OB 和骨细胞活性来降低 BMD。

2.2.2. 年龄影响

人类在 30 岁左右达到骨量峰值(peak bone mass, PBM)，峰值骨量是决定生命后期骨量和脆性骨折的关键因素[16]。Wang G 等[17]发现骨髓间充质干细胞(bone marrow mesenchymal stem cells, BMSC)是骨质疏松症骨恶化的关键，随着年龄的增长，器官和细胞衰老，BMSC 的减少使 OP 风险增加。He Y 等[18]通过一项对 2000 余名参与者横断面研究发现在中国初潮年龄超过 17 岁、绝经年龄小于 48 岁的女性患骨质疏松风险程度更高。Chandra A 等[19]发现随着年龄的增长，由骨骼形成和骨骼吸收之间的复杂平衡所维持的骨骼稳态受到氧化应激(Oxidative stress, OxS)调节。在 OxS 中反应性氧簇(Reactive oxygen cluster, ROC)的过度产生诱导 DNA 损伤，细胞凋亡和细胞衰老，促进 OC 的分化，使其介导的骨吸收大于 OB 的骨生成，造成骨稳态失衡。

2.2.3. 钙、维生素 D 影响

钙的吸收与沉积在骨组织维持骨量中起重要作用，推荐平均膳食钙摄入量为 1170 毫克/天[20]。维生素 D 可以增强肠道钙转运、肾小管对钙质的吸收来间接影响骨组织，血清 25-(OH)D < 50 nmol/L 会增加 OPF 风险，800 IU/d 的维生素 D 摄入可降低风险[21]。儿童佝偻病、骨软化症也由维生素 D 缺乏引起，对成人引起骨质疏松、继发性甲亢，并增加骨折的风险[22]。临床医生应注意妊娠相关骨质疏松症(Pregnancy associated osteoporosis, PAO)，在怀孕期间能量补充不足，钙剂及维生素 D 缺乏导致怀孕或产后出现新发腰背痛的女性，应特别考虑这种情况[23]。

2.2.4. 疾病及药物影响

骨质疏松可分为三类。① 由于年龄增长(老年性骨质疏松)或性腺功能减退(绝经后骨质疏松)引起称为原发性骨质疏松；② 疾病和药物因素下导致的继发性骨质疏松；③ 特发性骨质疏松，多发生在青年和遗传病史的人群中。在继发性骨质疏松中：疾病的发生，如甲状腺、胃肠、慢性肾病、肝病及尿毒症等疾病都会影响机体矿物质和维生素 D；感染性、自身免疫性和血液系统疾病中的促炎细胞因子可刺激 OC 成熟分化；若患者长期应用避孕药物或肝素、激素等容易导致骨质疏松[24]。

2.2.5. 肌量影响

肌肉减少症和骨质疏松症都是绝经后妇女的严重健康问题。骨骼肌指数(skeletal muscle index, SMI)有助于诊断严重骨质疏松症和脊柱后凸患者的肌肉减少症[25]。肌量减少导致绝经后、老年型骨质疏松患病风险增加[26]。肌肉和骨骼之间的耦合是根据机械传导，这表明施加到肌肉上的机械力会传递到骨骼以

启动骨重建[27]。年轻人因骨折使运动减少，老年人的衰老、运动量减少使肌肉强度、骨骼所受的机械应力减弱，因局部骨骼卸载或全身固定导致的骨质流失状态都是骨质疏松的危险因素，也称为废用性骨质疏松[28]。运动康复疗法可显著改善骨质疏松患者的症状和生活质量[29]。

2.2.6. 其他因素影响

不良生活习惯也和骨密度降低相关，如长期吸烟，高浓度咖啡，长期熬夜，偏食等，但证据程度较低；环境因素如较少的接受日照等；同时遗传因素可影响骨密度，但较罕见[30]。

2.3. 骨质疏松治疗

骨质疏松治疗首先进行生活方式调节，然后在钙剂和维生素 D 的基础上联合抗骨质疏松药物。目前药物根据作用分为三类：抗吸收药物、合成代谢药物及其他类。抗骨吸收药物的临床使用范围更广泛。

2.3.1. 生活方式调节

1) 规律作息和均衡膳食；2) 戒烟限酒，避免长期浓咖啡摄入；3) 增加日晒时长(>30 min/d)，规律运动，改善肌力；4) 提高机体灵活性及规避风险的反应性，降低跌倒风险。

2.3.2. 基础治疗

钙和维生素 D 在人体扮演重要角色。成人骨质疏松推荐 1000~1200 mg/d；成人正常维生素 D 400 IU (10 μg)/d，推荐 800~1200 IU/d 用于骨质疏松症防治时。不推荐一次补充大量维生素 D 或单纯钙剂联合维生素 D 治疗模式，需联合其他药物使用[31]。

2.3.3. 骨吸收抑制剂

① 双膦酸盐类，为 OP 的一线用药，通过作用法尼基焦磷酸合成酶诱导 OC 凋亡。长期应用增加非典型股骨骨折和下颌骨坏死发生风险，且老年患者胃肠道功能及肾功能不佳应慎用[32]；② 雌激素替代疗法：选择性雌激素受体调节剂(selective estrogen receptor modulator, SERMs)可降低绝经后女性雌激素撤退的不良影响。目前应用的药物为雷洛昔芬和巴多昔芬；③ 抑制核因子-kB 受体激活剂，地舒单抗与 RANK 竞争性结合 RANKL 抑制 OC 分化。最新的英国预防骨质疏松指南中提出地舒单抗可作为双膦酸盐等同的替代方案(强烈推荐) [33]；④ 降钙素(CT)，抑制 OC 的活性及骨溶解，为二线疗法；⑤ 去钙化醇(艾地骨化醇、阿法骨化醇、骨化三醇)是一种对骨吸收有很强抑制作用的维生素 D 类似物，可作为骨质疏松一级预防的良好候选药物[34]；⑥ 四烯甲萘醌，维生素 K2 同型物，对受雌激素撤退和糖皮质激素影响的 OP 有积极作用[35]。应用抗凝方案的患者需考虑后使用。

2.3.4. 骨形成促进剂

目前临床上通过促进骨形成发挥作用的药物主要有两种：① 甲状旁腺素(Parathyroid hormone, PTH)类似物，包括特立帕肽和阿巴洛肽，特立帕肽在增加 I 型前胶原的 N 端前肽(PINP)方面的排名优于其他干预措施，可减少骨折风险、增加 BMD 和促进骨形成[36]；② 骨硬化蛋白抑制剂(罗莫索珠单抗)，具有通过抑制硬化素来增加骨形成和减少骨吸收的双重作用，认为剂量作用最佳为 400 mg 时对骨促进作用更高，腰椎的 BMD 显着上升[37]。

2.3.5. 其他类药物

① 雷奈酸锶，合成锶盐，通过增加骨形成和减少骨吸收来保护骨组织，降低椎骨骨折的风险并增加 BMD；② 生长激素替代治疗，生长激素缺乏者会出现骨微结构破坏，给予替代治疗 6 月后骨量增加可达到顶点，并且联合双磷酸盐使用可更好的改善 BMD；③ 睾酮替代治疗，游离睾酮(CFT) < 7 ng/dl、生物有效性睾酮(BT) < 180 ng/dl 是骨质疏松的高危因素，睾酮替代治疗性腺功能减退患者，促进 OB 增值

分化[38]。

3. 地舒单抗

地舒单抗是美国安进(Amgen)公司寻求的抗 RANKL 抗体的药物，通过在基因水平上小鼠足垫免疫法获得。2010 年先后通过欧盟和美国审批用于因骨科疾病(骨质疏松、骨肿瘤、骨髓瘤等)导致的骨稳态失衡，骨质破坏；在我国主要用于绝经后骨质疏松妇女的治疗[39]。

3.1. 地舒单抗作用机制

人体骨组织的骨稳态中，OC 的骨吸收作用强于 OB 的骨形成是导致骨质疏松的关键因素。目前骨质疏松研究相关信号通路包括：Wnt/β-catenin 信号通路、Notch 通路、BMP 通路、SIRT1 通路、RANKL/RANK/OPG 通路等，其中 RANKL 通路及 Wnt/β-catenin 信号通路是药物研究治疗的热点[40]。同时发现骨质疏松机制中 RANKL/RANK/OPG 系统是影响 OC 活性的决定因素[41]。RANKL 与 RANK 结合使破骨前体细胞向 OC 分化。骨保护素(osteoprotegerin, OPG)竞争 RANKL 抑制 RANK 结合 RANKL，减少 OC 增值分化抑制骨吸收，使骨代谢趋向骨稳态平衡[42]。虽然 OPG 对 RANKL 的亲和力高于 RANK，但是其发挥作用所需的高剂量限制及较差的药效动力学使 OPG 不能作为很好的药物研究[43]。因此，OPG 类似物或 RANKL 抑制剂的药物研究成为主要方向。最终 Amgen 研发的 IgG2 单克隆抗体因其高度亲和力和较强的生物活性，并不存在 OPG 类似物诱导免疫反应带来的安全问题脱颖而出[39]。

3.2. 地舒单抗临床应用

到目前为止，在对地舒单抗临床应用疗效的研究中。为期 10 年的 FREEDOM 试验是规模最大的一项国际性研究，其采取的前瞻性，双盲对照，大样本研究的结论可作为地舒单抗临床应用的强力推荐证据。地舒单抗可持续增加绝经后骨质疏松症患者 BMD，降低患者骨折发生风险为椎体(68%)、髋部(40%)、非椎体(20%) [44]。单克隆抗体药物在提高骨密度方面比双膦酸盐类药物更为有效，因抑制骨转换的可逆性使药物作用没有平台期[45]。并且地舒单抗可显著降低患者死亡风险，对男性效果更显著[46]。在临床试验中，观察到地诺舒单抗的安全性及其在骨折复位方面的有效性与双膦酸类药物没有显著差异,服用地诺单抗的患者的骨密度(BMD)增加比服用双膦酸类药物的患者更有效[47] [48]。与双膦酸盐相比不良反应更少更轻，改善患者的偏好和依从性，并为高危或老年骨质疏松患者提供一种节省成本的治疗策略[49]。地舒单抗与现有的骨质疏松替代品和口服双磷酸盐(阿伦磷酸钠、雷奈酸锶、伊班磷酸钠)相比，具有显著的成本效益，尤其是老年妇女(>75 岁)及口服药物治疗方案依从性较差的情况下，地舒单抗可取得更好的临床疗效[50]。一项早期的回顾性分析中发现，非双磷酸盐与双膦酸盐对患者死亡率影响相差不大，对骨密度增加和骨折预防的临床为有益效果，其中非双膦酸盐的地舒单抗和罗莫佐单抗对髋部、股骨颈 BMD 提升最有效，特立帕肽对椎体的影响最大[51]。在最新的英国预防骨质疏松指南中提出，抗吸收药物治疗骨质疏松是一线选择，将静脉注射唑来膦酸盐作为髋部骨折首选治疗，并认为地舒单抗可作为其等同的替代方案(强烈推荐) [33]。跌倒是 OPF 独立危险因素，跌倒预防练习方案可较低跌倒发生率[33]。患者合并骨质疏松后，其骨折的风险程度增加[52]。Shi M 等研究表明，术前抗骨质疏松治疗可以减少假体周围骨丢失，降低并发症的风险[53]。骨质疏松症治疗与髋关节置换术后假体周围骨折的发生率较低相关，接受髋关节置换术的患者，应开始地舒单抗治疗，且不会影响骨折处愈合[54] [55]。骨质疏松程度与疼痛程度呈正相关，会显著降低生活质量，BMD 降低与休闲和社会活动成分之间的关系最强，双膦酸盐与地舒单抗治疗存在缓解疼痛的可能[56] [57]。发现地舒单抗对疼痛的缓解较阿仑磷酸钠更早期[58]。通过对 33 项研究包含 22,253 名患者的系统性评估中，认为地舒单抗治疗期间在耳、鼻、咽喉和胃肠道感染的发生

率较高，但相关死亡率的风险并不在增加[59]。地诺单抗的安全性和有效性在轻度至中度肾脏疾病的参与者中没有差异[60]。因此，地舒单抗可作为等同双膦酸盐对骨质疏松的治疗，对骨质疏松患者及早应用地舒单抗干预治疗能获得更好的疗效，地舒单抗的缓解疼痛的作用多采用疼痛视觉模拟量表(visual analogue score, VAS)这种主观评估方法，缺乏一定的客观性，这或许是地舒单抗的临床应用可更深入研究的一个方向。

3.3. 地舒单抗的序贯治疗

通过对地舒单抗和双膦酸盐疗效的系统评价发现地舒单抗既可作为治疗绝经后骨质疏松症的一线药物，也可作为双磷酸盐的替代药物。目前还没有足够的数据表明地舒单抗在预防骨折方面不逊于双膦酸盐类药物[61]。在预防骨折方面，停止使用地舒单抗后使多发椎体骨折风险增加[62]。重新开始使用地舒单抗并没有完全消除反弹相关的椎骨骨折风险，除特殊原因不建议停止用药[63]。这可能是地舒单抗在预防骨折较双膦酸盐较差的方面，因此，为了避免地舒单抗中断治疗的影响，序贯治疗是首先要考虑的事情。不建议双膦酸盐联合地舒单抗的治疗模式，但当因各种原因中断地舒单抗的治疗，需尽早补一针地舒单抗或使用双膦酸盐类药物作为地舒单抗停药后的序贯治疗是可接受的[64] [65]。同时罗莫唑单抗、特立帕肽、双膦酸盐后接续地舒单抗作为序贯治疗能很好的提高 BMD 及降低骨折风险，并认为先合成代谢物特立帕肽的使用再序贯骨吸收抑制剂地舒单抗的使用能取得更佳的疗效[66]。

3.4. 地舒单抗使用方法

每 6 个月在大腿、腹部或上臂经皮下注射 60 mg/1 次。

3.5. 地舒单抗相关不良反应

① 低钙血症：通过地舒单抗应用 5 年的随访发现，地舒单抗可引起低钙血症，且透析患者的低钙程度更严重，但地舒单抗对透析伴骨质疏松患者的疗效肯定且不受肾功能分期的影响[67]，因此需术前检测血钙水平并定期监测；② 感染风险：地舒单抗长期应用感染的风险较其余药物高，主要表现在耳、鼻、咽喉和胃肠道的感染[59]。③ 颌骨坏死：FREEDOM 试验中，使用地舒单抗 10 年长期组发现 7 例，3 年安慰剂组后使用 7 年地舒单抗交叉组发现 6 例，为罕见副反应，如果地舒单抗治疗期间有侵入性牙科治疗患者颌骨坏死的发生率更高[68] [69]。注意侵入性牙科治疗；④ 非典型股骨骨折：FREEDOM 试验中，长期组与交叉组中各发现 1 例[68]。单纯的骨质疏松患者用药期间注意有无大腿、髋部的疼痛感。⑤ 停药风险：停止使用地舒单抗后导致椎体骨折风险增加[62]，因此停药后序贯治疗是必须的。

4. 总结

在全球老龄化的背景下，骨质疏松患者逐渐增多且趋向老龄化，其干预治疗也受到更多的重视。患者主动体检检查骨密度的意识薄弱，多因难以忍受的疼痛或骨折后入院检查，同时医师需提高对骨质疏松患者的评估意识。在骨质疏松的药物治疗中，以抗骨吸收药物作为一线用药，虽然地舒单抗在我国上市时间短暂，但其国外长期的临床研究疗效得到肯定，可作为等同或者替代双膦酸盐在抗骨质疏松治疗药物中的一线地位。地舒单抗与双膦酸盐对骨密度的提高疗效、全因死亡率相近，虽然对降低骨折的风险未优于双膦酸盐，但是其副作用较双膦酸盐更低，且有更好的成本效益及患者依从性。在骨质疏松越来越被认为是一种长期病，慢性病的情况下，地舒单抗缓解疼痛、不影响骨折愈合、增加假体稳定性的积极作用使患者更受益。同时未发现有地舒单抗与国内中成药联合使用对骨密度的影响，其中西医合用的治疗方案，不仅使地舒单抗的应用中国化，也为中成药的抗骨质疏松提供新方案。随着地舒单抗在我国的临床应用，不再局限于绝经后骨质疏松女性，未来更大规模的多中心、大样本、前瞻性的临床试验

可用来证实地舒单抗的安全性和有效性，为患者治疗提供更多选择。

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