· 综述 ·

狄诺塞麦治疗代谢性骨病的研究进展

孔晶　王鸥　邢小平

【摘要】 狄诺塞麦(Denosumab)是人抗核因子-κB 受体活化因子配体(RANKL)的 IgG2 型单克隆抗体。它是治疗骨质疏松的第一种单克隆抗体药物,多个临床试验已证实,其可以抑制骨转换、提高骨密度以及降低骨折风险。目前也有少量研究发现,其对畸形性骨炎、骨纤维异常增殖症、成骨不全等其他代谢性骨病有较良好的疗效。

【关键词】 核因子-κB 受体活化因子配体;狄诺塞麦;骨质疏松;代谢性骨病

基金项目:国家自然科学基金资助项目(81270873);国家临床重点专科课题(WBYZ 2011-873)

Update on denosumab treatment in metabolic bone diseases

Kong Jing, *Wang Ou*, *Xing Xiaoping*. *Department of Endocrinology*, *Key Laboratory of Endocrinology*, *National Health and Family Planning Commission*, *Peking Union Medical College Hospital*, *Chinese Academy of Medical Science & Peking Union Medical College*, *Beijing* 100730, *China*

Corresponding author: *Xing Xiaoping*, *Email*: *xingxp*2006@126.*com*

【**Abstract**】 Denosumab is a human IgG2 monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL). It is the first monoclonal antibody agent to treat osteoporosis. Kinds of clinical trials showed that denosumab could suppress bone turnover, increase bone mineral density (BMD) and reduce the risk of fracture. Recently, denosumab has been found to be effective in other metabolic bone diseases, such as Paget's disease of bone, fibrous dysplasia and osteogenesis imperfecta.

【**Key words**】 Receptor activator of nuclear factor-kappa B ligand; Denosumab; Osteoporosis; Metabolic bone diseases

Fund program: National Natural Science Foundation of China (81100559); National Key Program of Clinical Science (WBYZ 2011-873)

狄诺塞麦(Denosumab)是一种人类 IgG2 型单克隆抗体,对核因子-κB 受体活化因子配体(RANKL)有高度的亲和力和专一性。RANKL由成骨细胞分泌,与破骨细胞及前体破骨细胞上的核因子-κB 受体活化因子(RANK)结合后,促进破骨细胞分化和活化,并抑制破骨细胞凋亡。狄诺塞麦通过竞争性结合RANKL,阻止其与RANK结合,从而抑制骨吸收。目前该药已被美国食品药品监督管理局批准用于治疗骨折风险高的绝经后骨质疏松妇女、男性骨质疏松、芳香化酶抑制剂治疗乳腺癌所致的骨量丢失以及前列腺癌应用去势治疗所致的骨量丢失。本文就狄诺塞麦治疗代谢性骨病的疗效进行综述。

1　绝经后骨质疏松

1.1　对骨转换标志物(BTMs)的影响　绝经后骨质疏松通常以骨转换水平增加、骨吸收超过骨形成为特征,FREEDOM(Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months)研究纳入 7 868例绝经后骨质疏松妇女,将其随机分至狄诺塞麦组(60 mg,1 次/6 月)或安慰剂组,与安慰剂组相比,狄诺塞麦组的 1 型胶原交联 C 末端肽水平在治疗 1 个月、6 个月及 36 个月时分别降低86%、72%及72%;1 型前胶原 N 端前肽水平则分别降低18%、50%及76%(n = 160)[1]。在FREEDOM延伸研究中,狄诺塞麦组继续接受 3 年的狄诺塞麦治疗(长期治疗组,n = 2 343),原安慰剂组改为接受狄诺塞麦治疗(交叉组,n = 2 207),发现长期治疗组的BTMs可持续被抑制,交叉组的 BTMs 可被迅速抑制,证实了狄诺塞麦长期应用对抑制BTMs的有效性[2]。

1.2　对骨密度的影响　FREEDOM 亚组研究(n = 441)发现,与安慰剂组相比,狄诺塞麦组治疗

DOI:10.3760/cma.j.issn.1673-4157.2016.05.13

作者单位:100730　北京,中国医学科学院,北京协和医学院,北京协和医院内分泌科,卫生及计划生育委员会内分泌重点实验室

通信作者:邢小平,Email: xingxp2006@126.com

36 个月后腰椎、全髋、股骨颈、大转子、桡骨远端 1/3 及全身骨密度分别增加9.2%、6.0%、4.8%、7.9%、3.5%和4.1%，表明狄诺塞麦可明显提高皮质骨及松质骨骨密度（$P<0.001$）[1, 3]。在FREEDOM延伸研究中，长期治疗组经过狄诺塞麦治疗 6 年后，各部位的骨密度均得到持续增加（腰椎：15.2%，全髋：7.5%，股骨颈：6.7%，桡骨远端 1/3：2.7%），腰椎、全髋及股骨颈骨密度与延伸期治疗前的基线相比明显增高（$P<0.05$）；此外，交叉组经过 3 年狄诺塞麦治疗后各部位的骨密度也明显升高（$P<0.05$，升幅与 FREEDOM 结果相似），该结果也提示，长达 6 年的狄诺塞麦治疗可持续性提高骨密度[2]。

骨强度由骨密度和骨质量决定，双能 X 线吸收测定法（DXA）得到的骨密度并未考虑体积对骨密度的影响，因此体积骨密度（vBMD）较面积骨密度能更真实反映骨密度。FREEDOM亚组研究使用定量 CT 发现，狄诺塞麦可以显著提高腰椎、髋骨及桡骨的皮质骨、松质骨以及皮质下骨的骨矿含量及vBMD，并可增加股骨及腰椎骨强度[4-5]。Brown 等[6]通过髂棘骨活检，在组织学水平上印证了狄诺塞麦可以降低骨转换、提高骨质量。

1.3　对骨折风险的影响　在降低骨折风险方面，FREEDOM研究发现，狄诺塞麦较安慰剂相比可显著降低椎体（2.3% *vs.* 7.2%，*RR* = 0.32，95% *CI*：0.26 ~ 0.41，$P<0.01$）、髋部（0.7% *vs.* 1.2%，*RR* = 0.60，95% *CI*：0.37 ~ 0.97，$P=0.04$）及非椎体骨折发生率（6.5% *vs.* 8.0%，*RR* = 0.80，95% *CI*：0.67 ~ 0.95，$P=0.01$）。FREEDOM研究的亚组分析还发现，狄诺塞麦降低非椎体骨折发生率的作用与股骨颈骨密度、体重指数以及既往骨折史相关，在股骨颈骨密度的 T 值≤ −2.5、体重指数 < 25 kg/m^{2}以及既往无骨折的人群中，狄诺塞麦降低非椎体骨折最显著，而降低椎体骨折率则不受以上因素影响[7]。狄诺塞麦延伸治疗 3 年间的新发椎体及非椎体骨折率分别为3.5%和3.8%，明显低于FREEDOM研究的安慰剂组及延伸治疗期的虚拟安慰剂组，但与FREEDOM研究前 3 年的狄诺塞麦组相仿，提示随着治疗时间的延长狄诺塞麦降低骨折的疗效并未降低[2]。

1.4　狄诺塞麦与双膦酸盐类药物（BPs）治疗绝经后骨质疏松的比较　虽然狄诺塞麦和BPs均为骨吸收抑制剂，但两者的作用机制和药效学特性等并不相同，临床应用有所差异：（1）狄诺塞麦作为一种抗体，通过网状内皮组织清除而非肾脏，因此其应用不受肾功能的限制[8]。（2）狄诺塞麦为皮下注射，可以避免口服BPs的消化道刺激症状，并且每年 2 次的注射频率可提高患者的依从性[9]。（3）疗效：DECIDE研究（The Determining Efficacy：Comparison of Initiating Denosumab versus Alendronate）头对头比较了狄诺塞麦和阿仑膦酸钠治疗绝经后骨量减少妇女的疗效，治疗 12 个月后狄诺塞麦较阿仑膦酸钠可进一步显著降低 BTMs 及增加各部位骨密度（P 均≤0.0002）[10]。一项荟萃分析提示，狄诺塞麦降低椎体骨折风险优于阿仑膦酸钠（*OR* = 1.67；95% *CI*：1.06 ~ 2.67），降低非椎体骨折方面两者无明显差异[11]。（4）药物假期：BPs紧密结合在骨基质中，一般认为停药后存在药物假期。而狄诺塞麦仅通过结合细胞外液或循环中的RANKL而发挥作用，因此狄诺塞麦的作用是可逆的，停药后BTMs迅速升高、降低骨折风险作用消失[12-13]。提示狄诺塞麦停用后需要应用其他抗骨质疏松药物来巩固疗效。

2　男性骨质疏松

ADAMO（A multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety of denosumab vs placebo in males with osteoporosis）研究纳入228例骨量减少男性（30 ~ 85岁），前 1 年受试者被随机分至狄诺塞麦组和安慰剂组，揭盲后安慰剂组改为接受 1 年狄诺塞麦治疗（交叉组），结果发现，经 2 年狄诺塞麦治疗的受试者血 1 型胶原交联 C 末端肽被抑制至基线水平的50%（$P<0.000\ 1$）、骨密度获得持续性提高（腰椎：8.0%，全髋：3.4%，股骨颈：3.4%，大转子：4.6%，桡骨远端 1/3：0.7%，P 均 <0.01），交叉组各部位骨密度增长幅度与狄诺塞麦组前 1 年相似[14]。目前暂无狄诺塞麦影响男性骨质疏松骨折风险方面的数据。

3　药物导致的骨质疏松

3.1　芳香化酶抑制剂（AIs）治疗乳腺癌导致的骨量丢失　对于雌激素受体阳性的乳腺癌患者，应用AIs是重要的辅助治疗措施，但AIs可通过降低雌激素水平促进骨吸收并增加骨折风险。另一方面，化学治疗所导致卵巢功能衰竭也促进乳腺癌患者的骨丢失。HALT-BC（the Hormone Ablation Bone Loss Trial in Breast Cancer）研究将应用AIs并且骨量减少的早期乳腺癌患者随机分至治疗组（狄诺塞麦60 mg，1 次/6 月）与安慰剂组，1 年后治疗组腰椎骨密度升高4.8%，而安慰剂组降低0.7%（$P<0.000\ 1$）；治疗

2 年后，两组腰椎骨密度的差异达 7.6%（$P<0.000\ 1$）；治疗组的全髋、股骨颈、桡骨 1/3 段以及全身骨密度均显著升高[15]。ABCSG-18 研究则发现，狄诺塞麦可延长雌激素受体阳性的绝经后早期乳腺癌患者的首次骨折发生时间（$HR=0.50$，95% CI：0.39～0.65，$P<0.000\ 1$），且两组间的不良反应发生率差异无统计学意义[16]。

3.2　雄激素去势治疗（ADT）治疗前列腺癌导致的骨量丢失　ADT 是转移性前列腺癌的一线治疗方案，也常应用于非转移性前列腺癌，ADT包括双侧睾丸切除术以及应用促性腺激素释放激素（GnRH）类似物。低雄激素状态会导致骨吸收增加、骨密度降低及骨折风险增加。HALT-PC（the Hormone Ablation Bone Loss Trial in Prostate Cancer）研究将应用 ADT 的非转移性前列腺癌患者随机分至治疗组（狄诺塞麦60 mg，1 次/6 月）与安慰剂组，治疗 2 年后，治疗组腰椎骨密度升高5.6%，而安慰剂组降低 1%（$P<0.001$）；此外，治疗组的全髋、股骨颈以及桡骨 1/3 段骨密度均显著升高；3 年后治疗组的椎体骨折率也明显低于对照组（分别为 3.9%、1.5%；$P=0.006$），两组间的不良反应发生率差异无统计学意义[17]。

对于肿瘤患者，狄诺塞麦除了可以防止因内分泌治疗而导致的骨量丢失，还能有效降低因肿瘤骨转移导致的骨骼相关事件（包括病理性骨折、脊髓压迫、高钙血症等）的发生率、延长前列腺癌患者的无骨转移时间[18-21]。

3.3　糖皮质激素导致的骨质疏松（GIOP）　Hofbauer 等[22]在小鼠中转入人RANKL基因使其表达RANKL，应用强的松导致其骨量丢失，给予狄诺塞麦（10 mg/kg，2 次/周）后发现小鼠的骨密度及骨强度均得以增加。人群研究方面，3 项狄诺塞麦治疗GIOP的随机对照试验正在进行（ClinicalTrials. gov 注册号：NCT01575873，NCT02418273，NCT01465568）。

4　在其他代谢性骨病中的应用

4.1　畸形性骨炎（PDB）　PDB 是以骨转换增加、骨膨大、骨结构异常，导致骨痛和骨骼畸形为特点的代谢性骨病。骨保护素是体内天然的RANKL拮抗剂及诱饵受体，它与RANKL结合后，阻断RANKL与RANK结合。编码骨保护素的 TNFRSF11B 基因突变可导致青少年型畸形性骨炎（Juvenile Paget's disease，JPD）。目前PDB的主要治疗药物为BPs或降钙素。由于狄诺塞麦作用于RANKL/RANK/骨保护素通路，理论上可在发病机制层面上治疗JPD。目前为止，总共报道了 3 例经BPs治疗后病情仍活动的JPD患者接受狄诺塞麦治疗，其骨痛得到缓解，BTMs降至正常[23-24]。提示狄诺塞麦治疗JPD的效果可能优于BPs，并可能成为PDB的另一有效治疗药物，但需要更多大样本研究证实。需要注意的是，在该类患者应用狄诺塞麦前应补充维生素 D 和钙剂以防止低钙血症的出现。

4.2　骨纤维异常增殖症（FD）　FD 是一种正常骨组织或骨基质被纤维组织替代，伴随破骨细胞活性增加的代谢性骨病。目前BPs为主要治疗药物，但仍有部分患者用药后骨痛症状无改善、BTMs未被抑制或者发生药物耐受[25]。鉴于FD病变组织存在RANKL过表达，有学者尝试应用狄诺塞麦治疗FD[26]。Boyce等[27]报道 1 例 9 岁患严重FD的男孩，其股骨病变经帕米膦酸钠治疗 1 年仍呈急剧进展，换用狄诺塞麦后，病变的生长速度明显减缓、骨痛缓解、BTMs被显著抑制，病变组织活检亦提示治疗后骨骼组织形态得到改善。另一研究也报道，3 例成人FD患者经长期唑来膦酸治疗无效，改为狄诺塞麦治疗后BTMs迅速被抑制，其中 1 例患者骨痛缓解[28-29]。上述 FD 患者在狄诺塞麦治疗期间血钙、磷、PTH水平波动较大，因此狄诺塞麦治疗过程中应密切监测并及时补充钙剂、维生素 D 和磷酸盐[27-28]。

4.3　成骨不全症（OI）　OI 是一种以骨骼脆性增加和骨量减少为主要特征的单基因遗传性疾病，目前主要采用BPs治疗以抑制骨吸收、降低骨折发生率。Ⅵ型 OI 是由SERPINF1基因突变引起，较其他类型 OI 对BPs的反应差[30]。Hoyer-Kuhn 等[31]将狄诺塞麦应用于 4 例经BPs治疗后 BTMs 仍高于正常的Ⅵ型 OI 患者，共观察 2 年，患者的BTMs被抑制、骨密度逐渐升高、椎体外形也得到改善，且药物的耐受性良好。此外，一项为期 48 周的狄诺塞麦治疗COL1A1或COL1A2基因突变所致 OI 的临床研究数据有待公布（ClinicalTrials. gov 注册号：NCT01799798）。另一项多中心临床研究正在进行（ClinicalTrials. gov 注册号：NCT02352753）。

5　安全性

FREEDOM 研究报道的狄诺塞麦总体不良反应与安慰剂组无明显差异，并未发现狄诺塞麦增加感染、肿瘤或心血管疾病发生的风险，亦未发现其导致骨折愈合延迟或低钙血症的情况[1]。在狄诺塞麦延长应用的 3 年间，所有不良事件发生率较前 3 年无明显统计差异，但有 6 例患者在应用3～4次的狄

诺塞麦后发生颌骨坏死,1 例患者发生了不典型股骨骨折,提示狄诺塞麦长期应用的安全性有待进一步评估,临床上应关注患者口腔及骨痛情况[2]。DECIDE研究报道的狄诺塞麦与阿仑膦酸钠应用 12 个月后,包括感染、肿瘤、骨折等不良事件发生率在两组间均未发现明显差异[10]。

6　展望

多项临床研究显示出狄诺塞麦在治疗绝经后骨质疏松的优势,它可以迅速抑制骨吸收、增加骨密度、减少骨折风险,还可改善骨微结构及增加骨强度。此外,狄诺塞麦可防治因内分泌治疗导致的骨量丢失,也可能在如畸形性骨炎、骨纤维异常增殖症以及成骨不全等罕见的代谢性骨病方面有应用价值。未来,需要更多的研究以评估其长期应用的安全性、与其他抗骨质疏松药物联合应用或序贯应用的价值。

参　考　文　献

[1] Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis[J]. N Engl J Med, 2009, 361(8): 756-765. DOI: 10.1056/NEJMoa0809493.

[2] Bone HG, Chapurlat R, Brandi ML, et al. The effect of three or six years of denosumab exposure in women with postmenopausal osteoporosis: results from the FREEDOM extension[J]. J Clin Endocrinol Metab, 2013, 98(11): 4483-4492. DOI: 10.1210/jc.2013-1597.

[3] BologneseæMA, Teglbjærg CS, Zanchetta JR, et al. Denosumab significantly increases DXA BMD at both trabecular and cortical sites: results from the FREEDOM study[J]. J Clin Densitom, 2013, 16(2): 147-153. DOI: 10.1016/j.jocd.2012.02.006.

[4] Genant HK, Libanati C, Engelke K, et al. Improvements in hip trabecular, subcortical, and cortical density and mass in postmenopausal women with osteoporosis treated with denosumab[J]. Bone, 2013, 56(2): 482-488. DOI: 10.1016/j.bone.2013.07.011.

[5] Keaveny TM, McClung MR, Genant HK, et al. Femoral and vertebral strength improvements in postmenopausal women with osteoporosis treated with denosumab[J]. J Bone Miner Res, 2014, 29(1): 158-165. DOI: 10.1002/jbmr.2024.

[6] Brown JP, Reid IR, Wagman RB, et al. Effects of up to 5 years of denosumab treatment on bone histology and histomorphometry: the FREEDOM study extension[J]. J Bone Miner Res, 2014, 29(9): 2051-2056. DOI: 10.1002/jbmr.2236.

[7] McClung MR, Boonen S, Törring O, et al. Effect of denosumab treatment on the risk of fractures in subgroups of women with postmenopausal osteoporosis[J]. J Bone Miner Res, 2012, 27(1): 211-218. DOI: 10.1002/jbmr.536.

[8] Jamal SA, Ljunggren O, Stehman-Breen C, et al. Effects of denosumab on fracture and bone mineral density by level of kidney function[J]. J Bone Miner Res, 2011, 26(8): 1829-1835. DOI: 10.1002/jbmr.403.

[9] Palacios S, Agodoa I, Bonnick S, et al. Treatment satisfaction in postmenopausal women suboptimally adherent to bisphosphonates who transitioned to denosumab compared with risedronate or ibandronate[J]. J Clin Endocrinol Metab, 2015, 100(3): E487-E492. DOI: 10.1210/jc.2014-3594.

[10] Brown JP, Prince RL, Deal C, et al. Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial[J]. J Bone Miner Res, 2009, 24(1): 153-161. DOI: 10.1359/jbmr.080901.

[11] Zhang L, Pang Y, Shi Y, et al. Indirect comparison of teriparatide, denosumab, and oral bisphosphonates for the prevention of vertebral and nonvertebral fractures in postmenopausal women with osteoporosis[J]. Menopause, 2015, 22(9): 1021-1025. DOI: 10.1097/GME.0000000000000466.

[12] Bone HG, Bolognese MA, Yuen CK, et al. Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass[J]. J Clin Endocrinol Metab, 2011, 96(4): 972-980. DOI: 10.1210/jc.2010-1502.

[13] Brown JP, Roux C, T rring O, et al. Discontinuation of denosumab and associated fracture incidence: analysis from the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial[J]. J Bone Miner Res, 2013, 28(4): 746-752. DOI: 10.1002/jbmr.1808.

[14] Langdahl BL, Teglbjærg CS, Ho PR, et al. A 24-month study evaluating the efficacy and safety of denosumab for the treatment of men with low bone mineral density: results from the ADAMO trial[J]. J Clin Endocrinol Metab, 2015, 100(4): 1335-1342. DOI: 10.1210/jc.2014-4079.

[15] Ellis GK, Bone HG, Chlebowski R, et al. Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer[J]. J Clin Oncol, 2008, 26(30): 4875-4882. DOI: 10.1200/JCO.2008.16.3832.

[16] Gnant M, Pfeiler G, Dubsky PC, et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial[J]. Lancet, 2015, 386(9992): 433-443. DOI: 10.1016/S0140-6736(15)60995-3.

[17] Smith MR, Egerdie B, Hernández Toriz N, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer[J]. N Engl J Med, 2009, 361(8): 745-755. DOI: 10.1056/NEJMoa0809003.

[18] Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study[J]. J Clin Oncol, 2010, 28(35): 5132-5139. DOI: 10.1200/JCO.2010.29.7101.

[19] Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma[J]. J Clin Oncol, 2011, 29(9): 1125-1132. DOI: 10.1200/JCO.2010.31.3304.

(下转第 341 页)

drome, and intima-media thickness in obese adolescent girls[J]. J Clin Endocrinol Metab, 2011, 96(11): 3533-3540. DOI: 10.1210/jc.2011-1609.
[15] Abazar E, Taghian F, Mardanian F, et al. Effects of aerobic exercise on plasma lipoproteins in overweight and obese women with polycystic ovary syndrome[J]. Adv Biomed Res, 2015, 4: 68. DOI: 10.4103/2277-9175.153892.
[16] Kiddy DS, Hamilton-Fairley D, Bush A, et al. Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome[J]. Clin Endocrinol (Oxf), 1992, 36(1): 105-111.
[17] Ornstein RM, Copperman NM, Jacobson MS. Effect of weight loss on menstrual function in adolescents with polycystic ovary syndrome[J]. J Pediatr Adolesc Gynecol, 2011, 24(3): 161-165. DOI: 10.1016/j.jpag.2011.01.002.
[18] Hoeger K, Davidson K, Kochman L, et al. The impact of metformin, oral contraceptives, and lifestyle modification on polycystic ovary syndrome in obese adolescent women in two randomized, placebo-controlled clinical trials[J]. J Clin Endocrinol Metab, 2008, 93(11): 4299-4306. DOI: 10.1210/jc.2008-0461.
[19] Vitek W, Hoeger KM. Treatment of polycystic ovary syndrome in adolescence[J]. Semin Reprod Med, 2014, 32(3): 214-221. DOI: 10.1055/s-0034-1371093.
[20] Mathur R, Levin O, Azziz R. Use of ethinylestradiol/drospirenone combination in patients with the polycystic ovary syndrome[J]. Ther Clin Risk Manag, 2008, 4(2): 487-492.
[21] Pehlivanov B, Mitkov M. Efficacy of an oral contraceptive containing drospirenone in the treatment of women with polycystic ovary syndrome[J]. Eur J Contracept Reprod Health Care, 2007, 12(1): 30-35.
[22] Guido M, Romualdi D, Giuliani M, et al. Drospirenone for the treatment of hirsute women with polycystic ovary syndrome: a clinical, endocrinological, metabolic pilot study[J]. J Clin Endocrinol Metab, 2004, 89(6): 2817-2823.
[23] Moghetti P, Tosi F, Tosti A, et al. Comparison of spironolactone, flutamide, and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial[J]. J Clin Endocrinol Metab, 2000, 85(1): 89-94.
[24] Castelo-Branco C, Del Pino M. Hepatotoxicity during low-dose flutamide treatment for hirsutism[J]. Gynecol Endocrinol, 2009, 25(7): 419-422.
[25] Fauser BC, Tarlatzis BC, Rebar RW, et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group[J]. Fertil Steril, 2012, 97(1): 28-38. e25. DOI: 10.1016/j.fertnstert.2011.09.024.
[26] Glintborg D, Altinok ML, Mumm H, et al. Body composition is improved during 12 months' treatment with metformin alone or combined with oral contraceptives compared with treatment with oral contraceptives in polycystic ovary syndrome[J]. J Clin Endocrinol Metab, 2014, 99(7): 2584-2591. DOI: 10.1210/jc.2014-1135.
[27] Escobar-Morreale HF, Carmina E, Dewailly D, et al. Epidemiology, diagnosis and management of hirsutism: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society[J]. Hum Reprod Update, 2012, 18(2): 146-170. DOI: 10.1093/humupd/dmr042.
[28] Ganie MA, Khurana ML, Nisar S, et al. Improved efficacy of low-dose spironolactone and metformin combination than either drug alone in the management of women with polycystic ovary syndrome (PCOS): a six-month, open-label randomized study[J]. J Clin Endocrinol Metab, 2013, 98(9): 3599-3607. DOI: 10.1210/jc.2013-1040.
[29] Ibáñez L, Valls C, Ferrer A, et al. Additive effects of insulin-sensitizing and anti-androgen treatment in young, nonobese women with hyperinsulinism, hyperandrogenism, dyslipidemia, and anovulation[J]. J Clin Endocrinol Metab, 2002, 87(6): 2870-2874.
[30] Escobar-Morreale HF, Botella-Carretero JI, Alvarez-Blasco F, et al. The polycystic ovary syndrome associated with morbid obesity may resolve after weight loss induced by bariatric surgery[J]. J Clin Endocrinol Metab, 2005, 90(12): 6364-6369.
[31] Eid GM, Cottam DR, Velcu LM, et al. Effective treatment of polycystic ovarian syndrome with Roux-en-Y gastric bypass[J]. Surg Obes Relat Dis, 2005, 1(2): 77-80.

(收稿日期:2015-09-27)

(上接第 338 页)

[20] Denosumab for the prevention of skeletal complications in metastatic castration-resistant prostate cancer: comparison of skeletal-related events and symptomatic skeletal events[J]. Ann Oncol, 2015, 26(6): 1274. DOI: 10.1093/annonc/mdv155.
[21] Smith MR, Saad F, Coleman R, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial[J]. Lancet, 2012, 379(9810): 39-46. DOI: 10.1016/S0140-6736(11)61226-9.
[22] Hofbauer LC, Zeitz U, Schoppet M, et al. Prevention of glucocorticoid-induced bone loss in mice by inhibition of RANKL[J]. Arthritis Rheum, 2009, 60(5): 1427-1437. DOI: 10.1002/art.24445.
[23] Polyzos SA, Singhellakis PN, Naot D, et al. Denosumab treatment for juvenile Paget's disease: results from two adult patients with osteoprotegerin deficiency ("Balkan" mutation in the TNFRSF11B gene)[J]. J Clin Endocrinol Metab, 2014, 99(3): 703-707. DOI: 10.1210/jc.2013-3762.
[24] Grasemann C, Schündeln MM, Hövel M, et al. Effects of RANK-ligand antibody (denosumab) treatment on bone turnover markers in a girl with juvenile Paget's disease[J]. J Clin Endocrinol Metab, 2013, 98(8): 3121-3126. DOI: 10.1210/jc.2013-1143.
[25] Chapurlat RD. Medical therapy in adults with fibrous dysplasia of bone[J]. J Bone Miner Res, 2006, 21(Suppl 2): P114-P119.
[26] Piersanti S, Remoli C, Saggio I, et al. Transfer, analysis, and reversion of the fibrous dysplasia cellular phenotype in human skeletal progenitors[J]. J Bone Miner Res, 2010, 25(5): 1103-1116. DOI: 10.1359/jbmr.091036.
[27] Boyce AM, Chong WH, Yao J, et al. Denosumab treatment for fibrous dysplasia[J]. J Bone Miner Res, 2012, 27(7): 1462-1470. DOI: 10.1002/jbmr.1603.
[28] Ganda K, Seibel MJ. Rapid biochemical response to denosumab in fibrous dysplasia of bone: report of two cases[J]. Osteoporos Int, 2014, 25(2): 777-782. DOI: 10.1007/s00198-013-2585-1.
[29] Benhamou J, Gensburger D, Chapurlat R. Transient improvement of severe pain from fibrous dysplasia of bone with denosumab treatment[J]. Joint Bone Spine, 2014, 81(6): 549-550. DOI: 10.1016/j.jbspin.2014.04.013.
[30] Becker J, Semler O, Gilissen C, et al. Exome sequencing identifies truncating mutations in human SERPINF1 in autosomal-recessive osteogenesis imperfecta[J]. Am J Hum Genet, 2011, 88(3): 362-371. DOI: 10.1016/j.ajhg.2011.01.015.
[31] Hoyer-Kuhn H, Netzer C, Koerber F, et al. Two years' experience with denosumab for children with osteogenesis imperfecta type Ⅵ[J]. Orphanet J Rare Dis, 2014, 9: 145. DOI: 10.1186/s13023-014-0145-1.

(收稿日期:2015-09-04)