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艾拉莫德对难治性类风湿关节炎患者骨密度和血清 B-ALP、CTX-I 的机制分析 *

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摘要 目的：探讨艾拉莫德对难治性类风湿关节炎患者骨密度和血清骨碱性磷酸酶（B-ALP）、I 型胶原交联羧基末端肽（CTX-I）的机制。**方法：**选择 2019 年 1 月至 2020 年 12 月我院接诊的 134 例难治性类风湿关节炎患者，通过随机数表法分为观察组和对照组，每组 67 例。对照组给予甲氨蝶呤联合依那西普治疗，观察组给予艾拉莫德片联合依那西普治疗，均连续治疗 12 周。比较两组临床缓解率、实验室指标、类风湿关节炎患者病情评价（DAS28 评分）、骨密度、血清 B-ALP、CTX-I 的变化和不良反应。**结果：**治疗后，观察组临床缓解率为 90.00%，明显高于对照组 72.50%（$P<0.05$）；观察组红细胞沉降率（ESR）、C 反应蛋白（CRP）、类风湿因子（RF）、抗环挂氨酸肽抗体（抗 -CCP）表达和 DAS28 评分分别为（23.53±2.77）mm/h、（11.73±2.30）mg/L、（17.45±3.08）U/L、（43.22±7.17）RU/mL、（2.74±0.34）分，均明显低于对照组的（31.27±5.04）mm/h、（19.11±2.12）mg/L、（24.47±2.59）U/L、（55.23±7.44）RU/mL、（3.21±0.50）分，差异有统计学意义（$P<0.05$）；观察组骨密度、血清 B-ALP 分别为（0.83±0.05）g/cm^3、（117.02±15.65）U/L，均明显高于对照组（0.77±0.04）g/cm^3、（101.19±9.59）U/L，观察组 CTX-I 为（0.36±0.04）μg/L，明显低于对照组（0.47±0.04）μg/L，差异有统计学意义（$P<0.05$）；两组不良反应总发生率分别为 4.44%和 2.22%，差异无统计学意义（$P>0.05$）。**结论：**艾拉莫德联合依那西普治疗难治性类风湿关节炎效果显著，可明显改善骨密度、血清 B-ALP、CTX-I 的表达，提高临床缓解率，安全性好，值得应用推广。

关键词：艾拉莫德；难治性类风湿关节炎；骨密度；骨碱性磷酸酶；I 型胶原交联羧基末端肽
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Analysis of the Mechanism of the Effect of Iguratimod on Bone Mineral Density and Serum B-ALP and CTX-I in Patients with Refractory Rheumatoid Arthritis*

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ABSTRACT Objective: To study the mechanism of the effect of iguratimod on bone mineral density and serum Bone alkaline phosphatase (B-ALP) and Type I collagen crosslinked carboxy terminal peptide (CTX-I) in patients with refractory rheumatoid arthritis. **Methods:** 134 patients of refractory rheumatoid arthritis who received therapy from January 2019 to December 2020 in our hospital were selected as research objects, according to the random number table, they were divided into the observation group and the control group, 67 cases in each group. The control group was treated with methotrexate combined with etanercept, and the observation group was treated with iguratimod combined with etanercept, they were continuous treatment 12 weeks. The clinical remission rate, laboratory indexes, disease evaluation (DAS28 score), bone mineral density, serum B-ALP, CTX-I and adverse reactions were compared between the two groups. **Results:** After treatment, the clinical remission rate in the observation group was 90.00%, significantly higher than the control group 72.50% ($P<0.05$); the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), anti cyclic peptide antibody (anti CCP) and DAS28 scores in the observation group were (23.53±2.77) mm/h, (11.73±2.30) mg/L, (17.45±3.08) U/L, (43.22±7.17) RU/mL, (2.74±0.34) scores respectively, which were significantly lower than the control group (31.27±5.04) mm/h, (19.11±2.12) mg/L, (24.47±2.59) U/L, (55.23±7.44) RU/mL, (3.21±0.50) scores , the difference were statistically significant ($P<0.05$); the bone mineral density and serum B-ALP in the observation group were (0.83±0.05) g/cm^3, (117.02±15.65) U/L, which were significantly higher than the control group (0.77±0.04) g/cm^3, (101.19±9.59) U/L, the CTX-I in the observation group were (0.36±0.04) μg/L, which were

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significantly lower than the control group (0.47±0.04) μg/L, the difference were statistically significant (P<0.05); the total incidence of adverse reactions in the two groups was 4.44% and 2.22% respectively, there were no significant difference (P>0.05). **Conclusion:** Iguratimod combined with etanercept is well for refractory rheumatoid arthritis, which can effectively improve the expression of BMD, serum B-ALP and CTX-I, improve the clinical remission rate, and has good safety, which is worth popularizing.

Key words: Iguratimod; Refractory rheumatoid arthritis; Bone mineral density; Bone alkaline phosphatase; Type I collagen crosslinked carboxy terminal peptide

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前言

类风湿关节炎是风湿免疫科中常见的一种慢性免疫性疾病[1,2]。该病发病因素尚未完全明确，可能和遗传、感染、性激素等相关，患者以炎性滑膜炎为主要表现，严重者可出现关节畸形甚至功能丧失[3,4]。抗风湿药物（DMARDs）是治疗该病的常用方案，但临床上仍有部分患者在接受超过 6 个月的 2 种或 2 种以上的 DMARDs 联合治疗后临床症状仍未明显改善，称为难治性类风湿关节炎，此类患者不仅治疗难度更大，预后也更差[5,6]。艾拉莫德是一类抗风湿新药，具有抗炎、免疫调节等作用，近年来其在类风湿关节炎患者中的应用价值也逐渐受到诸多学者关注[7,8]。因此，本研究旨在探讨艾拉莫德在难治性类风湿关节炎患者的应用效果，并观察其对骨密度和血清骨碱性磷酸酶（B-ALP）、I 型胶原交联羧基末端肽（CTX-I）的机制，现报道如下。

1 资料与方法

1.1 一般资料

选择 2019 年 1 月至 2020 年 12 月我院接诊的 134 例难治性类风湿关节炎患者，纳入标准[9,10]：（1）符合美国风湿病学会修订的诊断标准，a、晨僵时间 1h 以上（≥ 6 周），b、3 个或以上的关节受累（≥ 6 周），c、手部关节受累（≥ 6 周），d、对称性关节炎（≥ 6 周），e、类风湿皮下结节，f、X 线片显示软组织肿胀等，g、血清类风湿因子结果为阳性，上述 7 项符合≥ 4 项则可确诊；（2）关节功能分级 II~III 级；（3）经 2 种或 2 种以上 DMARDs（甲氨蝶呤、柳氮磺吡啶、来氟米特、硫酸羟氯喹）治疗 6 个月以上病情仍处于活动期，无明显改善；（4）签署本研究知情同意书。排除标准[11,12]：（1）骨关节炎、痛风性关节炎、银屑病关节炎、强直性脊柱炎或其余疾病所致的关节炎；（2）合并呼吸衰竭、心力衰竭、恶性高血压、恶性肿瘤肝肾功能严重损伤等；（3）合并急慢性感染、活动性结核病、乙型病毒性肝炎等；（4）合并神经系统病变；（5）既往使用过艾拉莫德；（6）妊娠期哺乳期或处于备孕阶段的男性女性；（7）对研究药物过敏；（8）中途退出研究或失访。通过随机数表法分为观察组和对照组，每组 67 例，两组一般资料见表 1，差异无统计学意义（P>0.05）。研究已通过我院伦理委员会批准实施。

表 1 两组一般资料比较[$\bar{x}\pm s$，n(%)]

Table 1 Comparison of general data between the two groups[$\bar{x}\pm s$, n(%)]

Groups	n	Gender(M/F)	Age(years)	BMI(kg/m^2)	Course of disease (years)	Classification of joint function	
						II	III
Observation group	67	46/21	54.72±7.40	21.86±2.40	8.64±2.41	45(67.16)	22(32.84)
Control group	67	50/17	55.05±7.11	21.97±2.21	8.55±2.79	48(71.64)	19(28.36)

1.2 方法

对照组给予甲氨蝶呤片（规格 2.5 mg，厂家：上海信谊药厂有限公司，国药准字 H31020644），剂量 10 mg/ 周，依那西普注射液（规格 12.5 mg，厂家：三生国健药业（上海）股份有限公司，批准文号 S20050058），剂量 25 mg 皮下注射，2 次 / 周；观察组给予艾拉莫德片（规格 25 mg，厂家：先声药业有限公司，国药准字 H20110084）治疗，25 mg/ 次，2 次 /d，依那西普剂量 25 mg 皮下注射，2 次 / 周。两组均连续治疗 12 周。

1.3 观察指标

1.3.1 **临床缓解率** 参照文献[13]评价，下述 6 项符合其中 5 项且维持时间＞2 个月则判定为临床缓解，a、晨僵时间＜15 min，b、无疲劳感，c、无关节疼痛感，d、无关节压痛感或活动时无关节疼痛，e、无关节或腱鞘肿胀症状，f、红细胞沉降率（ESR）检查显示，女＜30 mm/h，男＜20 mm/h。

1.3.2 **实验室指标** 采集所有受试者治疗前、治疗后 10 mL 空腹静脉血，置于 3000 r/min 的条件下，离心 5 min 后提取血清液待检，使用魏氏法检测 ESR，免疫比浊法检测 C 反应蛋白（CRP），速率散射比浊法检测类风湿因子（RF），酶联免疫吸附法（ELISA）检测抗环挂氨酸肽抗体（抗 -CCP），所使用的试剂盒均购于上海基尔顿生物科技有限公司。

1.3.3 **类风湿关节炎患者病情评价（DAS28 评分）** 根据关节压痛数、关节肿胀数、ESR 等结果，参照公式计算，DAS28=[0.56×关节压痛数 +0.28×关节肿胀数 +0.70×In（ESR）]×1.08÷0.16。

1.3.4 **骨密度** 使用美国 ALARA 数字化成像骨密度仪 MetriScanTM 检测，检测部位食指、中指、无名指指骨，其中 T＞-1.0 标准差（S）表示正常，-2.5S=T＜-1.0S 则表示骨量减少，T＜-2.5S 则表示骨质疏松。

1.3.5 **血清 B-ALP、CTX-I** 均使用南京建成生物公司生产的酶联免疫吸附法试剂盒检测。

1.3.6 **安全性** 记录治疗期间不良反应情况。

1.4 统计学分析

以 spss18.0 软件包处理，计量资料用($\bar{x}\pm s$)表示，组间比较使用独立样本 t 检验，组内比较使用配对样本 t 检验，计数资料以率表示，χ^2 检验，$P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组临床缓解率比较

观察组临床缓解率明显高于对照组($P<0.05$)，见表 2。

表 2 两组临床缓解率比较

Table 2 Comparison of clinical remission rate between the two groups

Groups	n	Remission cases	Remission rate(%)
Observation group	67	61	91.04
Control group	67	51	76.12
χ^2 value			5.438
P value			0.020

2.2 两组实验室指标、DAS28 评分比较

治疗后，两组 ESR、CRP、RF、抗 -CCP 表达和 DAS28 评分均明显低于治疗前($P<0.05$)，观察组 ESR、CRP、RF、抗 -CCP 表达和 DAS28 评分均明显低于对照组($P<0.05$)，见表 3。

表 3 两组实验室指标、DAS28 评分比较($\bar{x}\pm s$)

Table 3 Comparison of laboratory index and DAS28 score between the two groups($\bar{x}\pm s$)

Groups	n	Time	ESR(mm/h)	CRP(mg/L)	RF(U/L)	Anti-CCP (RU/mL)	DAS28 score (score)
Observation group	67	Before treatment	58.32±7.61	40.12±4.64	64.44±7.30	154.42±27.50	5.42±0.75
		After treatment	23.53±2.77*	11.73±2.30*	17.45±3.08*	43.22±7.17*	2.74±0.34*
Control group	67	Before treatment	57.85±8.22	40.65±4.20	63.61±7.62	153.21±29.61	5.35±0.88
		After treatment	31.27±5.04*#	19.11±2.12*#	24.47±2.59*#	55.23±7.44*#	3.21±0.50*#

Note: Vs with before treatment, *$P<0.05$; Vs with observation group, #$P<0.05$.

2.3 两组骨密度、血清 B-ALP、CTX-I 比较

治疗后，两组骨密度、血清 B-ALP 均明显高于治疗前，CTX-I 明显降低($P<0.05$)，观察组骨密度、血清 B-ALP 均明显高于对照组，CTX-I 明显比对照组低($P<0.05$)，见表 4。

表 4 两组骨密度、血清 B-ALP、CTX-I 比较($\bar{x}\pm s$)

Table 4 Comparison of Bone mineral density, serum B-ALP, CTX-I between the two groups($\bar{x}\pm s$)

Groups	n	Time	Bone mineral density (g/cm^3)	B-ALP(U/L)	CTX-I(μg/L)
Observation group	67	Before treatment	0.72±0.08	73.32±6.40	0.60±0.05
		After treatment	0.83±0.05*	117.02±15.65*	0.36±0.04*
Control group	67	Before treatment	0.71±0.08	72.56±6.72	0.61±0.05
		After treatment	0.77±0.04*#	101.19±9.59*#	0.47±0.04*#

Note: Vs with before treatment, *$P<0.05$; Vs with observation group, #$P<0.05$.

2.4 安全性评价

两组治疗期间均未发生严重不良事件，观察组出现 1 例氨基转移酶升高，给予护肝片口服后恢复正常，另有 1 例恶心呕吐，对照组有 1 例恶心呕吐患者，两组总发生率分别为 4.44% 和 2.22%，差异无统计学意义($\chi^2=0.345$，$P=0.557$)。

3 讨论

类风湿关节炎是一种系统性免疫疾病，好发于女性，可造成人体血管、滑膜等出现炎症反应，多数患者以慢性、对称性的关节炎为主要表现，随着疾病的进展，可对关节软骨造成破坏，致使关节肿胀、畸形等，甚至活动功能丧失[14,15]。目前仍无针对类风湿关节炎的特效药物，临床上多选择非甾体抗炎药(NSAIDs)、DMARDs 等单用或联合治疗，但也有部分患者在接受长期的治疗后症状无明显缓解，进展成难治性类风湿关节炎[16,17]。

目前针对难治性类风湿关节炎患者的治疗通常采取 DMARDs 联合生物制剂单药治疗[18,19]。甲氨蝶呤是其中较为常用的 DMARDs 药物，可通过对二氢叶酸还原酶产生抑制作用，阻碍四氢叶酸的活化，继而抑制细胞 DNA 的合成和增殖，但甲氨蝶呤也有骨髓抑制、胃肠道反应、肝肾功能损伤等副作用，不适宜长期大剂量的应用[20,21]。依那西普是一种肿瘤坏死因子(TNF-α)抑制剂，适用于对甲氨蝶呤在内的 DMARDs 药物治

疗无效的类风湿关节炎患者，可和甲氨蝶呤联合使用[22,23]。但也有研究显示仍有部分患者难以达到临床缓解，疗效有提升空间[24,25]。艾拉莫德是种新型抗风湿药物，主要是通过抑制炎症因子、免疫球蛋白等发挥药效，有研究指出，艾拉莫德兼具NSAIDs、DMARDs的抗炎、抗风湿的双重疗效，不失为难治性类风湿关节炎的良好选择[26,27]。也有研究将艾拉莫德联合生物制剂的报道显示，其可有效改善类风湿性关节患者的关节活动程度[28]。

血清B-ALP、CTX-I是反映骨组织代谢的指标，其中B-ALP可了解成骨细胞活动期、骨形成过程，其浓度的降低代表新骨形成的速率减慢，而在骨吸收过程中，骨质中的I型胶原会出现降解，导致CTX-I在血液中的大量释放，导致其浓度增加，可反映骨破坏程度[29,30]。而在类风湿关节炎患者中，软骨和骨降解呈现出持续且反复的状态，随着成骨细胞的减少、破骨细胞的不断分化，可进一步对患者骨密度产生不利影响，降低预后[31,32]。本研究结果显示，艾拉莫德联合依那西普的患者在骨密度、血清B-ALP、CTX-I的改善程度上明显更为优异，通过分析是由于艾拉莫德具有促骨形成、抗骨吸收的效果，可刺激成骨细胞分化和骨的构建，并抑制破骨细胞的生成。有报道显示，艾拉莫德可通过降低基质金属蛋白酶-1的表达，对滑膜成纤维细胞的侵袭产生抑制作用，发挥骨保护作用[33]。且本研究中艾拉莫德联合依那西普的患者在临床缓解率、实验室指标、DAS28评分的结果上效果也更明显，显示出该方式在治疗难治性类风湿患者的疗效更加明显，且艾拉莫德和甲氨蝶呤的作用环节不同，可弥补甲氨蝶呤所缺乏的抗炎效果，进一步提高关节骨关节保护效果，提高疗效。但难治性类风湿关节炎患者的治疗是一个漫长的过程，对于更远期的疗效及安全性方面仍需持续探讨。

综上所述，艾拉莫德联合依那西普治疗难治性类风湿关节炎效果显著，可明显改善骨密度、血清B-ALP、CTX-I的表达，提高临床缓解率，安全性好，值得应用推广。

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