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依那西普联合甲氨蝶呤治疗类风湿关节炎疗效分析

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摘要 目的:探讨依那西普联合甲氨蝶呤治疗类风湿关节炎的疗效。**方法:**选取 2011 年至 2013 年风湿免疫科的 60 例类风湿关节炎患者,分为对照组和治疗组,其中对照组 15 例,治疗组 45 例,两组患者都应用甲氨蝶呤治疗,治疗组患者联合使用依那西普治疗,总疗程 12 周。比较两组患者治疗前后的临床及实验室指标。采用美国风湿病学会的核心标准作为疗效评定标准。**结果:**治疗组患者肿瘤坏死因子(tumor necrosis factor, TNF)和白细胞介素(interleukin, IL-1)下降明显,与对照组患者相比差异均有统计学意义($P < 0.05$);治疗后两组患者超敏 C 反应蛋白(hs-CRP)均较治疗前明显降低,差异均有统计学意义($P < 0.05$);治疗组患者关节疼痛、关节肿胀和晨僵情况较对照组均有显著的改善($P < 0.05$);治疗组患者的休息痛、患者评分以及 HAQ 评分均显著优于对照组($P < 0.05$);治疗组患者 ACR20 和 ACR70 缓解的比例均高于对照组,且治疗组患者达 ACR50 缓解的比例显著高于对照组($P < 0.05$)。**结论:**依那西普联合甲氨蝶呤治疗类风湿关节炎的疗效优于单纯的甲氨蝶呤治疗。

关键词:类风湿关节炎;依那西普;甲氨蝶呤;疗效

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Curative Effect Analysis on Etanercept Combined with Methotrexate in the Treatment of Rheumatoid Arthritis

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ABSTRACT Objective: To explore the curative effect of etanercept combined with methotrexate in the treatment of rheumatoid arthritis (RA). **Methods:** 60 patients with RA were selected from 2011 to 2013 and divided into the control group and treatment group. 15 patients in control group and 45 patients in treatment group were all treated with methotrexate, what's more, the patients of treatment group were treated with etanercept at the same time. The course of treatment was 12 weeks. The clinical and laboratory indexes of these two groups of patients before and after the treatment were compared. The American College of Rheumatology (ACR) criteria was used for clinical assessments. **Results:** The TNF and IL-1 of the treatment group significantly decreased and had statistical significance, when compared with patients of control group ($P < 0.05$). The hs-CRP of both two groups were significantly reduced after treatment ($P < 0.05$). The joint pain, joint swelling and morning stiffness of the treatment group were significantly improved than in control group ($P < 0.05$). The rest pain, patients' VAS and HAQ scores of the treatment group were significantly better than those of control group ($P < 0.05$). The ACR20, ACR70 responses of the treatment group were better than those of control group, and the ACR50 responses were significantly better than those of control group ($P < 0.05$). **Conclusion:** Compared with methotrexate, etanercept combined with methotrexate had significant efficacy in patients with RA.

Key words: Rheumatoid arthritis; Etanercept; Methotrexate; Curative effect

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前言

类风湿关节炎 (rheumatoid arthritis, RA) 是一种临床多发、常见病以及疑难病^[1,2],它是以一种关节滑膜炎为特征的累及周围关节为主的异质性、系统性、炎症性、多发性的自身免疫性疾病。RA 一种是常见的高发病率、高致残率的风湿性疾病,据统计^[3,4],RA 患者在发病的最初 2 年即可出现不可逆的骨质破坏,随着病情的进展逐渐丧失劳动力,严重影响患者的生活

质量。RA 的发病过程伴随着多种炎症细胞因子的活化^[5],其中,肿瘤坏死因子(tumor necrosis factor, TNF)和白细胞介素(interleukin, IL-1)是 RA 发病中占中心地位的促炎因子,在介导 RA 炎症反应和导致组织损伤中起重要作用^[6,7]。针对 RA 的治疗尚无根治手段,早期多采用甲氨蝶呤等传统药物改善患者病情,但仍有很多患者不能有效改善病情。近年来,通过阻断 TNF 和 IL-1 来阻断 RA 的炎症反应,从而达到治疗 RA 的应用广泛^[8],TNF 拮抗剂依那西普可缓解 RA 病情^[9,10],但与甲氨蝶呤联用治疗的报道不多,本文介绍应用依那西普联合甲氨蝶呤治疗类风湿关节炎的疗效,现报告如下。

1 资料与方法

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1.1 一般资料

选取 2011 年至 2013 年风湿免疫科的 60 例类风湿关节炎患者。入选标准:所有患者均符合美国风湿病协会(ACR)1987 年修订的 RA 诊断标准,且病情处在活动期;所有患者均自愿参加本次试验;未使用任何其他生物制剂治疗,4 周内未使用过糖皮质激素治疗、未服用 DMARDs、1 周内未使用 NASIDs;排除伴有严重心、肝、肾损害、处于急性或慢性感染急性发作期、恶性肿瘤、孕妇或哺乳期妇女以及患有内分泌疾病的患者。将 60 例患者随机分为对照组和治疗组,其中对照组 15 例,治疗组 45 例。对照组男 3 例,女 12 例;平均年龄(44.3 ± 4.8)岁;病程(9.2 ± 2.9)年;治疗组男 5 例,女 40 例;平均年龄(44.8 ± 4.9)岁;病程(8.9 ± 3.0)年。两组患者在性别、年龄、病程方面比较,差异均无统计学意义($P > 0.05$),资料具有可比性。

1.2 方法

两组患者均口服甲氨蝶呤(methotrexate, MTX, 上海信宜制药总厂, 2.5 mg/片)10 mg, 每周 1 次,外加非甾体消炎药(西乐葆/乐松);治疗组患者加用依那西普(etanercept, Enbrel, 上海中信国健药业有限公司)25 mg, 每周 2 次,采用皮下注射的方式,外加非甾体消炎药(西乐葆/乐松),试验总疗程 12 周。在治疗前后抽取两组患者的清晨空腹肘静脉血 3 mL, 分离血清后采用酶联免疫吸附测定法集中检测血清 TNF 和 IL-1 的水平。记录并比较两组患者的主要症状变化、TNF 和 IL-1 指标及观察指标数据,包括关节疼痛评分、关节肿胀评分、晨僵时间、TNF 水平、IL-1 水平、患者对休息痛及目前疾病总体状况的自我评分(VAS)、医生对患者疾病总体状况的评分(VAS)、健康评估问卷(HAQ)和急性期反应物(CRP)。采用美国风湿病学会(ACR)的核心疗效评价,应用 ACR20、ACR50 和 ACR70 来评价药物疗效。

1.3 评定标准

(1)关节疼痛/肿胀评分标准:0 分:无痛/无肿胀;1 分:有压痛/轻微肿胀;2 分:有压痛伴随皱眉和不适/中度肿胀;3 分:压痛剧烈且患者有躲避检查的动作/明显肿胀。(2)患者/医生对目前疾病状况的评分:采用视觉模拟标尺评分法(VAS),使用一条约 100 mm 的游动标尺,从 0~100,疼痛程度由无痛~难以忍受的最剧烈的疼痛,由患者/医生对用药前后综合状态做一个评估,在标尺上标出相应得分。(3)健康评估问卷(Health assessment question-naire, HAQ):由患者对自身日常生活能力包括穿衣、吃喝、站立、行走等 20 项指标进行评估,研究者记录评估结果。(4)ACR20 的定义:患者关节压痛及肿胀个数有 20%的改善以及患者对休息痛及目前疾病总体状况的自我评分(VAS)、医生对患者疾病总体状况的评分(VAS)、健康评估问卷(HAQ)和急性期反应物(CRP),这 5 项中至少有 3 项有 20%的改善。ACR50、ACR70 定义相同。

1.4 统计学分析

采用 SPSS 18.0 统计软件建立数据库,计量资料以均数 $\pm$ 标准差($\bar{x} \pm s$)表示;两组资料比较时采用 t 检验及卡方检验进行统计分析。检验水准 $\alpha=0.05$ 。

2 结果

2.1 两组患者治疗前后实验室检查结果比较

由表 1 可知,两组患者治疗前血清中的 TNF 及 IL-1 的浓度比较差异不明显,差异均无统计学意义($P > 0.05$)。12 周的疗程治疗后,治疗组患者血清中的 TNF 及 IL-1 的浓度较对照组均明显降低,差异均有统计学意义($P < 0.05$)。治疗组患者治疗后血清中的 TNF 及 IL-1 的浓度较治疗前均明显降低,差异均有统计学意义($P < 0.05$),对照组患者治疗后血清中的 IL-1 较治疗前显著降低($P < 0.05$)。

表 1 两组患者治疗前后实验室检查结果比较($\bar{x} \pm s$)

Table 1 Comparison of laboratory results after and before treatment between two groups($\bar{x} \pm s$)

组别 Groups	TNF(pg/ml)		IL-1(pg/ml)	
	治疗前 Before treatment	治疗后 After treatment	治疗前 Before treatment	治疗后 After treatment
治疗组(n=45) Treatment group(n=45)	20.2 $\pm$ 11.9	12.1 $\pm$ 5.6*	49.3 $\pm$ 16.6	23.2 $\pm$ 9.2*
对照组(n=15) Control group(n=45)	19.4 $\pm$ 10.3	16.3 $\pm$ 7.1	48.7 $\pm$ 15.9	32.4 $\pm$ 9.6*
t	0.233	2.349	0.123	3.319
P	0.817	0.022	0.903	0.002

注:*)与治疗前相比 $P < 0.05$ 。

Note:*)Compared with before treatment $P < 0.05$.

2.2 两组患者治疗后主要症状比较

由表 2 可知,经 12 周疗程治疗后,治疗组患者关节疼痛、关节肿胀和晨僵这三个主要症状较对照组均有显著的改善,差异均具有统计学意义($P < 0.05$)。

2.3 两组患者治疗前后观察指标的比较

两组患者治疗前各观察指标差异均不明显($P > 0.05$)。两

组患者经 12 周的疗程治疗后各观察指标较治疗前均有显著的改善($P < 0.05$),其中,经 12 周的疗程后治疗组患者的休息痛、患者评分以及 HAQ 评分显著优于对照组,差异均有统计学意义($P < 0.05$),详见表 3。

2.4 两组患者治疗后 ACR 疗效的比较

由表 4 可知,经 12 周疗程治疗后,治疗组患者 ACR20 和

表 2 治疗后两组患者主要症状比较($\bar{x} \pm s$)Table 2 Comparison of cardinal symptoms after treatment between two groups($\bar{x} \pm s$)

组别 Groups	关节疼痛评分(分) Joint pain score(score)	关节肿胀评分(分) Joint swelling score(score)	晨僵时间(h) Morning stiffness time(h)
治疗组(n=45) Treatmeat group(n=45)	0.8± 0.3	0.9± 0.4	0.5± 0.2
对照组(n=15) Control group(n=45)	1.7± 0.6	2.0± 0.4	1.3± 0.5
t	5.582	9.224	6.038
P	0.001	0.001	0.001

表 3 两组患者治疗前后观察指标的比较($\bar{x} \pm s$)Table 3 Comparison of observation indexes after and before treatment between two groups($\bar{x} \pm s$)

指标 Indexes	组别 Groups	治疗前 Before treatment	治疗后 After treatment
休息痛(mm) The rest pain(mm)	治疗组(n=45) Treatmeat group(n=45)	83± 15	23± 15 ^{##}
	对照组(n=15) Control group(n=45)	82± 13	35± 20 [#]
	治疗组(n=45) Treatmeat group(n=45)	86± 14	22± 14 ^{##}
患者评分(mm) Patients' VAS (mm)	对照组(n=15) Control group(n=45)	85± 13	34± 18 [#]
	治疗组(n=45) Treatmeat group(n=45)	83± 13	23± 12 [#]
	对照组(n=15) Control group(n=45)	79± 15	30± 18de
医生评分(mm) Doctors'VAS (mm)	治疗组(n=45) Treatmeat group(n=45)	2.1± 0.6	0.3± 0.2 ^{##}
	对照组(n=15) Control group(n=45)	2.0± 0.7	0.5± 0.3 [#]
	治疗组(n=45) Treatmeat group(n=45)	53± 36	9± 7 [#]
CRP(mm/L)	对照组(n=15) Control group(n=45)	45± 23	11± 7 [#]

注:*)与对照组相比 P<0.05; #)与治疗前相比 P<0.05。

Note: *)Compared with control group P<0.05; #)Compared with before treatment P<0.05.

ACR70 缓解的比例均高于对照组,但差异均无统计学意义。组,差异有统计学意义(P<0.05)。(P>0.05),治疗组患者达 ACR50 缓解的比例显著高于对照

表 4 治疗后两组患者 ACR 疗效比较(n;%)

Table 4 Comparison of ACR effect after treatment between two groups(n;%)

组别 Groups	例数 Cases	ACR20	ACR50	ACR70
治疗组(n=45) Treatmeat group(n=45)	45	35(77.8)	29(64.4)	16(35.6)
对照组(n=15) Control group(n=45)	15	10(66.7)	4(26.7)	2(13.3)
χ^2		0.741	6.487	2.646
P		0.494	0.016	0.192

3 讨论

类风湿关节炎是一种炎症性、慢性的全身性免疫疾病^[11,12],如不经治疗,大部分 RA 患者会发生关节损害甚至残疾。

近年来,国内外相关研究^[13-15]均表明,TNF 和 IL-1 受体拮抗剂可通过减轻炎症及关节的破坏,从而缓解 RA 病情,TNF 在 RA 的发病中占非常重要的地位,抗 TNF 可以直接中和循环中的组织中的可溶性 TNF,从而减轻组织的损伤。依那西普(注射用重组人 II 型肿瘤坏死因子受体-抗体融合蛋白)由 II 型 TNF 受体 P75 的细胞外部分和人 IgG1 的 Fc 段融合而成^[16],与循环中的可溶性 TNF 相结合,通过阻断其与组织细胞表面的 TNF 受体结合,从而达到减少组织损伤的目的。TNF 拮抗剂依那西普的临床疗效优于传统的 DMARDs 药物,且与甲氨蝶呤联用的效果更佳^[17],本研究证实,12 周的疗程治疗后,治疗组患者血清中的 TNF 浓度较对照组明显降低($P < 0.05$),治疗组患者治疗后血清中的 TNF 的浓度较治疗前明显降低($P < 0.05$),与国内外相关研究结论一致。

本次研究资料显示,治疗 12 周后,治疗组患者的主要症状,包括关节疼痛、关节肿胀、晨僵时间的改善情况均明显优于对照组($P < 0.05$),提示依那西普联合甲氨蝶呤治疗组的效用显著优于单纯性甲氨蝶呤治疗的对照组,这与相关文献报道是一致的^[18]。

本次研究结果显示,治疗 12 周后,治疗组患者休息痛、患者评分以及 HAQ 评分指标均显著优于对照组($P < 0.05$);治疗组患者 ACR20 和 ACR70 缓解的比例均高于对照组,且治疗组患者达 ACR50 缓解的比例显著高于对照组($P < 0.05$)。提示,依那西普联合甲氨蝶呤以及单纯性的甲氨蝶呤对 RA 都有治疗作用,但依那西普联合甲氨蝶呤的治疗组起效时间明显比对照组早,且治疗组达到 ACR 缓解的 RA 患者比例要显著高于对照组,它的疗效明显比对照组更优。

总而言之,依那西普联合甲氨蝶呤治疗 RA,能快速并有效地改善 RA 患者的临床症状、实验室指标以及观察指标等情况。传统的单纯性抗风湿药物甲氨蝶呤等治疗 RA 的疗效令人不甚满意,同时,大量研究证明患者使用这类药物后不良反应严重^[19,20],依那西普联合甲氨蝶呤治疗 RA 的疗效较单纯性的甲氨蝶呤更优,效果令人满意,在今后的临床工作中,还需进一步深入的了解依那西普联合甲氨蝶呤治疗 RA 的疗效和不良反应,为 RA 患者制定有针对性的个体化治疗方案。

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