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甲氨蝶呤联合来氟米特对类风湿关节炎患者炎症因子和免疫球蛋白的影响*

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摘要 目的：探讨甲氨蝶呤联合来氟米特对类风湿关节炎（RA）患者炎症因子和免疫球蛋白的影响。**方法：**选取于2016年6月-2017年10月期间我院收治的92例RA患者，根据乱数表法将患者随机分为对照组（n=46）与研究组（n=46）。对照组给予口服甲氨蝶呤片，研究组则在对照组的基础上联合来氟米特片治疗。两组均治疗3个月。比较两组患者临床疗效、临床症状改善情况，检测两组患者治疗前后炎症因子、免疫球蛋白水平，观察两组患者不良反应发生情况。**结果：**研究组患者治疗后的临床总有效率为95.65%（44/46），高于对照组患者的78.26%（36/46）（P<0.05）。两组患者治疗后晨僵时间、压痛关节数、肿胀关节数均较治疗前降低，且研究组低于对照组（P<0.05）。两组患者治疗后血细胞沉降率（ESR）、C反应蛋白（CRP）、白介素-8（IL-8）及肿瘤坏死因子（TNF-α）均较治疗前降低，且研究组低于对照组（P<0.05）。两组患者治疗后免疫球蛋白G（IgG）、免疫球蛋白A（IgA）、免疫球蛋白M（IgM）均较治疗前降低，且研究组低于对照组（P<0.05）。两组患者不良反应发生率比较无差异（P>0.05）。**结论：**甲氨蝶呤联合来氟米特治疗RA患者效果优于单用甲氨蝶呤治疗，可改善患者临床症状，同时降低IgG、IgA、IgM以及炎症因子水平，无严重不良反应发生。

关键词：甲氨蝶呤；来氟米特；类风湿关节炎；炎症因子；免疫球蛋白；疗效

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Effect of Methotrexate Combined with Leflunomide on Inflammatory Factors and Immunoglobulin in Patients with Rheumatoid Arthritis*

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ABSTRACT Objective: To investigate the effect of methotrexate combined with leflunomide on inflammatory factors and immunoglobulin in patients with rheumatoid arthritis (RA). **Methods:** A total of 92 patients with RA, who were treated in the 148th Hospital of PLA from June 2016 to October 2017, were selected and were randomly divided into control group (n=46) and study group (n=46). The control group was given oral Methotrexate Tablets, and the study group was treated with Leflunomide Tablets on the basis of the control group's therapy. The two groups were treated for 3 months. The clinical efficacy and the improvement of clinical symptoms were compared between the two groups. The inflammatory factors and immunoglobulin of the two groups were tested before and after treatment, and the incidence of adverse reactions in the two groups was observed. **Results:** The total effective rate [95.65% (44/46)] of the study group after treatment was significantly higher than that[78.26% (36/46)] of the control group (P<0.05). The time of morning stiffness, tender joint count, swollen joint count in the two groups after treatment was lower than before treatment, and the study group was lower than the control group (P<0.05). After treatment, the blood sedimentation rate (ESR),C reactive protein (CRP), interleukin-8 (IL-8) and tumor necrosis factor-α (TNF-α) in the two groups were all lower than those before treatment, and the study group was lower than that in the control group (P<0.05). After treatment, immunoglobulin G (IgG), immunoglobulin A (IgA) and immunoglobulin M (IgM) in the two groups were all lower than those before treatment, and the study group was lower than the control group (P<0.05). There was no significant difference in the incidence of adverse reactions between the two groups (P>0.05). **Conclusion:** Methotrexate combined with leflunomide in the treatment of RA patients is better than methotrexate alone, it can significantly improve the clinical symptoms and immune function, and reduce IgG, IgA, IgM and inflammatory factors at the same time, without serious adverse reaction.

Key words: Methotrexate; Leflunomide; Rheumatoid arthritis; Inflammatory factors; Immunoglobulin; Curative effect

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前言

类风湿关节炎（Rheumatoid arthritis，RA）是一种慢性、以炎

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性滑膜炎为主的全身免疫性疾病,临床主要表现为对称性多关节肿胀、晨僵、疼痛以及体重减轻等症状,严重者可导致关节畸形甚至功能丧失,给患者带来巨大的困扰[1-3]。因此,针对 RA 患者寻求快速有效的治疗方式具有重要的临床意义。目前临床上关于 RA 的治疗是以控制病情、改善关节功能为主,甲氨蝶呤是临床上治疗 RA 的首选药物,然而若长期使用该药物,患者容易发生骨髓抑制等多种并发症,且大量使用不利于患者预后[4-6]。来氟米特作为一种新型的免疫调节剂,可发挥抗炎、改善 RA 患者症状、减少骨关节破坏的功效,现已逐渐被临床应用[7-9]。鉴于此,本研究通过探讨甲氨蝶呤联合来氟米特对 RA 患者炎症因子和免疫球蛋白的影响,现作如下报道。

1 资料与方法

1.1 一般资料

选取于 2016 年 6 月 -2017 年 10 月期间我院收治的 RA 患者 92 例为研究对象。纳入标准[10]:(1)入选患者均符合美国风湿病协会所制定的有关 RA 的相关诊断标准;(2) 所有患者均符合以下诊断标准:晨僵时间超过 45min,肿胀关节数 3 个以上,压痛关节数 5 个以上,C 反应蛋白 (C reactive protein,CRP)超过正常值上限的 1.5 倍,血细胞沉降率(blood sedimentation rate,ESR)超过 30 mm/h;(3)对本次研究使用药物无禁忌症者;(4)患者及其家属对本研究知情同时签署了同意书。排除标准:(1)伴其他结缔组织病变者;(2)妊娠哺乳期妇女;(3)伴恶性肿瘤、肝肾功能障碍者;(4)合并心血管疾病者。根据随机数表法将患者分为对照组(n=46)与研究组(n=46)。其中对照组男 21 例,女 25 例,年龄 35-66 岁,平均(46.87± 4.68)岁;病程 2 个月 -3 年,平均(1.53± 0.87)年。研究组男 22 例,女 24 例,年龄 36-64 岁,平均(45.17± 5.01)岁;病程 4 个月 -3 年,平均(1.48± 0.82)年。两组患者一般资料比较无差异(P>0.05),本次研究符合我院伦理委员会制定的相关规定,并已获得批准。

1.2 治疗方法

两组患者治疗前均停用之前的治疗药物,如中药、激素等,均停止用药 2w 以上。随后对照组给予口服甲氨蝶呤片(湖南正清制药集团股份有限公司,国药准字 H19983205 ,规格:2.5 mg),10-15 mg/ 次,1 次 /w;研究组则在对照组的基础上联合来氟米特片(河北万岁药业有限公司,国药准字 H2008005,规格:10 mg)治疗,20 mg/ 次,1 次 /d,持续 3d,后增加剂量至 50 mg/ 次,1 次 /d。所有患者治疗疗程均为 3 个月。

1.3 观察指标

(1)临床疗效 观察两组患者治疗后(治疗 3 个月后)的临床疗效。疗效判定标准[11]:临床症状消失显示治愈;临床症状恢复 70%-99%显示显效;临床症状恢复 30%-69%显示有效;临床症状无改善甚至加重显示无效。总有效率为有效率、显效率、治愈率之和。(2)临床症状 比较两组患者治疗前后的晨僵时间、压痛关节数、肿胀关节数等临床症状。(3)炎症因子以及免疫球蛋白 分别于治疗前后采集患者清晨空腹静脉血 3 mL,速率 3000 r/min,离心时间 7 min,取上清液,存于 -70℃冰箱中待测。采用酶联免疫吸附试验检测 ESR、CRP、白介素 -8(Interleukin-8,IL-8)及肿瘤坏死因子(Tumor necrosis factor-α,TNF-α)水平,试剂盒来源于上海雅培生物科技工程有限公司。采用免疫比浊法检测免疫球蛋白 G(Immunoglobulin G,IgG)、免疫球蛋白 A(Immunoglobulin A,IgA)、免疫球蛋白 M(Immunoglobulin M,IgM)水平,试剂盒来源于浙江夸克生物科技有限公司。(4)不良反应 记录患者在治疗期间出现的不良反应。

1.4 统计学方法

研究数据经 SPSS25.0 软件处理,炎症因子、免疫球蛋白水平等计量资料用($\bar{x}\pm s$)表示,行 t 检验,临床总有效率等计数资料以(%)表示,行 x^2 检验,检验标准α=0.05。

2 结果

2.1 两组患者临床疗效比较

治疗后研究组临床总有效率为 95.65%(44/46),高于对照组患者的 78.26%(36/46)(P<0.05),见表 1。

表 1 两组患者临床疗效比较[n(%)]

Table 1 Comparison of the clinical efficacy of the two groups[n(%)]

Groups	n	Cure	Effective	Good	Invalid	Total effective rate
Control group	46	7(15.22)	14(30.43)	15(32.61)	10(21.74)	36(78.26)
Study group	46	14(30.43)	19(41.30)	11(23.91)	2(4.35)	44(95.65)
x^2	-					6.133
P	-					0.013

2.2 两组患者临床症状改善程度比较

两组患者治疗前晨僵时间、压痛关节数、肿胀关节数比较差异无统计学意义(P>0.05);两组患者治疗后晨僵时间、压痛关节数、肿胀关节数均较治疗前降低,且研究组低于对照组(P<0.05);详见表 2。

2.3 两组患者炎症因子比较

两组患者治疗前 ESR、CRP、IL-8 以及 TNF-α 比较差异无统计学意义 (P>0.05);两组患者治疗后 ESR、CRP、IL-8 以及 TNF-α 均较治疗前降低,且研究组低于对照组(P<0.05);详见表 3。

2.4 两组患者免疫球蛋白比较

两组患者治疗前 IgG、IgA 以及 IgM 比较差异无统计学意义(P>0.05);两组患者治疗后 IgG、IgA 以及 IgM 均较治疗前降低,且研究组低于对照组(P<0.05);详见表 4。

2.5 两组不良反应发生情况比较

观察组出现不良反应 6 例,其中谷丙转氨酶升高合并皮疹 3 例,恶心呕吐 1 例,腹痛 2 例,不良反应发生率为 13.04%(6/46);对照组出现不良反应 7 例,其中谷丙转氨酶升高合并

皮疹 2 例，恶心呕吐 2 例，腹痛 3 例，不良反应发生率为 15.22%(7/46)；两组患者不良反应发生率比较无差异(x^2=0.090,P=0.765)。

表 2 两组患者治疗前后临床症状改善情况比较($\bar{x}\pm s$)

Table 2 Comparison of clinical symptoms before and after treatment between two groups($\bar{x}\pm s$)

Groups	n	Time of morning stiffness(h)		Tender joint count(n)		Swollen joint count(n)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	46	2.73± 0.51	1.27± 0.61*	22.56± 5.26	14.58± 3.21*	19.23± 5.07	9.89± 1.94*
Study group	46	2.68± 0.47	0.79± 0.42*	23.16± 4.82	6.73± 2.78*	18.92± 4.85	5.03± 1.85*
t	-	0.489	4.396	0.570	12.538	0.300	12.296
P	-	0.626	0.000	0.561	0.000	0.765	0.000

Note: compared with before treatment, *P<0.05.

表 3 两组患者治疗前后炎症因子比较($\bar{x}\pm s$)

Table 3 Comparison of inflammatory factors before and after treatment between two groups($\bar{x}\pm s$)

Groups	n	ESR(mm/h)		CRP(mg/L)		IL-8(ng/mL)		TNF-α(pg/mL)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	46	32.69± 7.47	21.83± 8.24*	24.83± 5.68	13.27± 4.01*	0.79± 0.24	0.51± 0.21*	17.65± 4.21	8.49± 1.73*
Study group	46	33.71± 6.52	15.32± 7.51*	23.94± 6.25	8.02± 4.29*	0.81± 0.26	0.36± 0.15*	18.23± 3.84	4.23± 1.85*
t	-	0.698	3.960	0.715	6.064	0.383	3.942	0.691	11.407
P	-	0.487	0.000	0.477	0.000	0.702	0.000	0.491	0.000

Note: compared with before treatment, *P<0.05.

表 4 两组患者治疗前后免疫球蛋白比较($\bar{x}\pm s$,g/L)

Table 4 Comparison of immunoglobulin before and after treatment between two groups ($\bar{x}\pm s$,g/L)

Groups	n	IgG		IgA		IgM	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	46	21.89± 2.58	15.44± 3.11*	3.93± 1.27	2.71± 1.09*	2.86± 0.52	1.72± 0.37*
Study group	46	22.46± 2.33	12.03± 2.68*	3.72± 1.05	2.13± 1.33*	2.75± 0.63	1.31± 0.21*
t		1.112	5.633	0.864	2.288	0.913	6.536
P		0.269	0.000	0.390	0.025	0.364	0.000

Note: compared with before treatment, *P<0.05.

3 讨论

RA 是一种机体对滑膜组织产生免疫反应的自身免疫疾病，发病率较高，一般女性发病多于男性[12,13]。通常 RA 患者由于关节功能受损、生活自理遭到不同程度限制，继而导致患者负性情绪重，且病情持续周期长，治疗费用昂贵，给患者及其家属带来极大的心理以及经济负担[14,15]。甲氨蝶呤可抑制二氢叶酸还原酶活性，从而抑制细胞 DNA 的生物合成，并且具有免疫和抗炎的作用，临床上通常选用甲氨蝶呤治疗 RA 患者[16,17]，但有研究显示[18]，针对 RA 患者采用甲氨蝶呤治疗，关节肿痛可得到一定的缓解作用，然而其效果并不持久，一旦停药，短期内病情或可复发，临床疗效一般。而来氟米特是异恶唑类抗风湿药物，可通过抑制二氢乳清酸脱氧酶活性，对 T 细胞增殖有明显的抑制作用，保护机体免疫功能[19,20]，周平等人研究报道[21]，来氟米特可以延缓关节结构的破坏，对 RA 患者病情程度具有显著地改善作用，且能改善患者免疫功能。

本研究中结果发现，研究组的临床总有效率高于对照组，且治疗后晨僵时间、压痛关节数、肿胀关节数低于对照组，提示针对 RA 患者使用甲氨蝶呤联合来氟米特治疗效果优于单用甲氨蝶呤治疗，且临床症状改善更为明显，可能是两种药物发挥药效机制不同，且作用于身体的不同部位，两者联合应用可大大提高临床疗效。另有相关研究证实[22]，在 RA 的病理发生过程当中，RA 患者的滑膜血管存在免疫失调等现象，进一步引发滑膜血管炎症反应，导致血液中炎症因子水平升高。本研究结果表明两组患者治疗后 ESR、CRP、IL-8 及 TNF-α 均较治疗前降低，且研究组低于对照组(P<0.05)。表明甲氨蝶呤虽具有一定的抗炎作用，但甲氨蝶呤联合来氟米特治疗改善 RA 患者炎症因子水平更为明显，由于 ESR、CRP、IL-8 及 TNF-α 水平的降低，均能反映患者体内炎症递质的降低，患者体内上述四种指标的改善，对炎症消除以及血管通透性具有较好的恢复作

用。分析其作用机制,甲氨蝶呤可抑制 DNA 的生物合成,同时具有抗炎功能,而来氟米特属于抗增生活性免疫抑制剂,二者联合使用发挥协同作用,从而对患者病情起到缓解作用[23,24]。另外两组患者治疗后 IgG、IgA 以及 IgM 均较治疗前降低,且研究组低于对照组(P<0.05)。提示甲氨蝶呤联合来氟米特治疗可显著改善 RA 患者免疫功能,一方面是由于来氟米特可抑制络氨酸激酶减少嘧啶、二氢乳清酸脱氢酸的产生,导致 DNA 合成受到抑制,从而对淋巴细胞活化、免疫反应发挥药效机制,增强患者免疫功能[25-27];另一方面来氟米特联合甲氨蝶,可抑制淋巴细胞增殖,主要是由于来氟米特可在淋巴细胞分裂的早 G1 期发挥作用,而甲氨蝶呤则可在淋巴细胞分裂的晚 G1 期发挥药效,最终改善 RA 患者异常的免疫反应[28-30]。同时两组患者不良反应发生率比较无差异。提示甲氨蝶呤联合来氟米特无不良副作用,安全性较好。

综上所述,甲氨蝶呤联合来氟米特治疗 RA 患者,疗效满意,可明显改善患者临床症状,增强患者免疫功能,降低患者炎症因子水平,安全可靠。

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