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糖皮质激素联合吗替麦考酚酯分散片对系统性红斑狼疮患者的疗效 及对免疫功能的影响*

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摘要 目的: 研究糖皮质激素联合吗替麦考酚酯分散片治疗系统性红斑狼疮患者的临床疗效及对免疫功能的影响。**方法:** 选取2014年9月至2015年8月本院收治的84例系统性红斑狼疮患者,根据投硬币法分为观察组和对照组,42例每组。对照组使用单纯的糖皮质激素,观察组在此基础上使用吗替麦考酚酯分散片。比较两组患者临床疗效,治疗前后免疫球蛋白A(IgA)、免疫球蛋白G(IgG)、免疫球蛋白M(IgM)、C反应蛋白(CRP)、血沉(ESR)的变化及不良反应的发生情况。**结果:** 治疗后,观察组临床总有效率显著高于对照组($P<0.05$)。治疗前,两组患免疫球蛋白A(IgA)、免疫球蛋白G(IgG)、免疫球蛋白M(IgM)、C反应蛋白(CRP)、血沉(ESR)水平比较差异均无统计学意义($P>0.05$);治疗后,两组患者IgA、IgG、IgM、CRP、ESR水平均较治疗前显著降低($P<0.05$),与对照相比,观察组的IgA、IgG、IgM、CRP、ESR明显降低($P<0.05$)。两组的不良反应率比较差异无统计学意义($P>0.05$)。**结论:** 糖皮质激素联合吗替麦考酚酯分散片能有效改善系统性红斑狼疮患者的免疫功能,临床疗效良好,安全性高。

关键词: 糖皮质激素; 吗替麦考酚酯分散片; 系统性红斑狼疮; 免疫指标

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Clinical Efficacy of Glucocorticoid Combined with Mycophenolate Mofetil Capsules in Treatment of Systemic Lupus Erythematosus and Its Effect on Immune Function*

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ABSTRACT Objective: To study the clinical effect of glucocorticoid combined with mycophenolate mofetil tablets on the systemic lupus erythematosus and its effect on the immune function. **Methods:** Forty-eight patients with systemic lupus erythematosus treated admitted in our hospital from September 2014 to August 2015 were randomly divided into the observation group and the control group. The control group was treated by glucocorticoid alone, and the observation group was given mycophenolate tablets on the basis of control group. The levels of immunoglobulin A (IgA), immunoglobulin (IgG), immunoglobulin (IgM), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) and the occurrence of adverse effects were compared between two groups before and after treatment. **Results:** After treatment, the total effective rate of observation group was significantly higher than that of the control group ($P<0.05$). Before treatment, there was no significant difference in the immunotherapy (IgA), immunoglobulin (IgG), immunoglobulin (IgM), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) between the two groups ($P<0.05$). After treatment, the levels of IgA, IgG, IgM, CRP and ESR in the two groups were significantly lower than those before treatment ($P<0.05$). Compared with the control group, IgA, IgG, IgM, CRP and ESR in the observation group were lower ($P<0.05$). There was no significant difference in the adverse reaction rate between two groups ($P>0.05$). **Conclusion:** Glucocorticoids combined with mycophenolate mofetil dispersion tablets could effectively improve the immune function of patients with systemic lupus erythematosus with high safety.

Key words: Glucocorticoid; Mycophenolate mofetil dispersion tablets; Systemic lupus erythematosus; Immunological index

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前言

系统性红斑狼疮在临床中是一种较为典型的自身免疫性疾病,发病病因较为复杂,主要特征为大量自身抗体的产生,特

别是抗核抗体,以至于机体的各部位伴有沉积的免疫复合物,会对多系统器官造成累及性影响,包括呼吸、血液、神经、皮肤等器官^[1]。抗体和自身抗原形成免疫复合物作为自身免疫性疾病的共同病理基础,会激活补体系统,会损伤多器官,不但会有

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自身抗体产生,还会产生细胞因子、免疫细胞等免疫异常,其中NK细胞、B细胞、T细胞等淋巴细胞亚群均会对疾病造成一定影响^[2]。伴随着糖皮质激素在临床中的大量使用,其治疗系统性红斑狼疮中有所突破,然而由于药量大,副作用较为明显,大多数患者基本上难以实现较好的治疗效果^[3]。吗替麦考酚酯分散片属于一种较为新型的免疫抑制剂,可有效阻碍免疫活性^[4]。本研究主要就糖皮质激素联合吗替麦考酚酯分散片对系统性红斑狼疮患者的疗效及对免疫功能的影响进行分析如下。

1 资料与方法

1.1 临床资料

选取2014年9月至2015年8月期间本院收治的84例系统性红斑狼疮患者。纳入标准:①患者的临床诊断均和《系统性红斑狼疮诊断及治疗指南》^[5]中的标准相符;②依从性较好,可配合医护人员完成本次试验研究;③临床资料完善者。排除标准:①中途退出治疗者;②对本次研究中所使用的药物具有禁忌症的患者;③血管系统疾病或心肺功能严重障碍者;④中途退出本次试验的患者。整个研究均在患者及其家属知情同意下完成。根据投硬币法将本次研究对象分为观察组和对照组,42例每组。其中,观察组中女性38例,男性4例;年龄为26~64岁,平均 (41.23 ± 3.12) 岁;活动性指数分级:22例为轻度活动,15例为中度活动,5例为重度活动。对照组中女性36例,男性6例;年龄为27~65岁,平均 (41.31 ± 3.19) 岁;活动性指数分级:20例为轻度活动,16例为中度活动,6例为重度活动。两组患者性别、年龄、活动性指数分级临床资料比较差异无统计学意义($P>0.05$),具有可比性。

1.2 治疗方法

对照组使用单纯的糖皮质激素完成治疗,第1周服用泼尼松(生产厂家:浙江仙琚制药股份有限公司,规格:5 mg $\times$ 100 s,生产批号:20140204),40 mg/次,1次/天;第2周服用30 mg/次的泼尼松,1次/天,随后逐渐减量,同时服用羟氯喹(生产厂

家:上海中西制药有限公司,规格:0.2 g,生产批号:20140304),0.2 g/次,2次/天。观察组在对照组治疗基础上使用吗替麦考酚酯分散片(生产厂家:杭州中美华东有限公司,规格:0.25 g $\times$ 40 s,生产批号:20140508)完成治疗,0.5 g/次,2次/天。所有患者均需连续治疗1个月。

1.3 观察指标

1.3.1 临床疗效评价 经治疗后,患者的主要临床症状完全消失,检测指标完全达到正常水平,则为痊愈;经治疗后,活动性指数下降程度 $\geq 1/3$,检验指标基本上和缓解条件相符,并且连续服药病情趋于稳定状态则为显效;经治疗后,活动性指数下降程度 $\geq 1/3$ 但 $<2/3$,检测指标仅有部分属于缓解状态则为有效;经治疗后,患者的临床症状虽然有所改善,但不稳定,活动性指数下降程度 $<1/3$,并且由活动指征则为无效^[6]。总有效=痊愈+显效+有效。

1.3.2 免疫指标分析 使用动态免疫散射比浊法对患者免疫球蛋白A(IgA)、免疫球蛋白(IgG)、免疫球蛋白(IgM)、C反应蛋白(CRP)水平进行检测,BNP特种蛋白仪以及相配套的试剂均由美国德灵公司生产,使用魏氏血沉检测患者血沉(ESR),由姜堰市荣飞器械厂提供魏氏血沉管以及特制的血沉架。

1.3.3 分析不良反应 观察和记录两组患者在治疗中是否有带状疱疹、尿路感染、胃肠道反应、脱发等不良反应发生。

1.4 统计学分析

本次实验数据处理选择SPSS11.5软件包进行,计量资料用 $(\bar{x} \pm s)$ 来表示,采用t检验,计数资料用 $n(\%)$ 表示,采取 χ^2 检验,以 $P<0.05$ 表明差异具有统计学意义。

2 结果

2.1 两组患者临床疗效比较

治疗后,观察组临床总有效率显著高于对照组[92.86%(39/42)比73.81%(31/42)]($P<0.05$),见表1。

表1 两组患者临床疗效比较[例(%)]

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

Groups	Cases	Cured	Markedly	Effective	Invalid	The total effective
Observation group	42	24(57.14)	9(21.43)	6(14.29)	3(7.14)	39(92.86)*
Control group	42	16(38.10)	3(7.14)	12(28.57)	11(26.19)	31(73.81)

Note: Compared with control group, * $P<0.05$.

2.2 两组治疗前后免疫指标的比较

治疗前,两组患者IgA、IgG、IgM、CRP、ESR水平比较差异无统计学意义($P>0.05$);治疗后,两组患者IgA、IgG、IgM、CRP、

ESR水平较治疗前显著降低($P<0.05$),与对照相比,观察组的IgA、IgG、IgM、CRP、ESR水平较低($P<0.05$),见表2。

表2 两组治疗前后免疫指标的比较 $(\bar{x} \pm s)$

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

Items	Observation group(n=42)		Control group(n=42)	
	Before treatment	After treatment	Before treatment	After treatment
IgA(g/L)	3.24 $\pm$ 0.53	2.15 $\pm$ 0.31**	3.28 $\pm$ 0.57	2.78 $\pm$ 0.43*
IgG(g/L)	15.32 $\pm$ 2.54	10.98 $\pm$ 1.23**	15.39 $\pm$ 2.62	13.45 $\pm$ 2.03*
IgM(g/L)	2.04 $\pm$ 0.34	1.13 $\pm$ 0.12**	2.07 $\pm$ 0.35	1.56 $\pm$ 0.25*
CRP(g/L)	52.12 $\pm$ 4.87	5.87 $\pm$ 0.98**	52.19 $\pm$ 5.02	14.56 $\pm$ 2.43*
ESR(mm/h)	38.43 $\pm$ 3.21	9.43 $\pm$ 0.97**	38.51 $\pm$ 3.18	19.32 $\pm$ 1.87*

Note: Compared with before treatment, * $P<0.05$; Compared with control group after treatment, ** $P<0.05$.

2.3 两组患者不良反应发生情况的比较

在观察组中,1例患者出现带状疱疹,1例患者发生尿路感染,2例患者出现胃肠道反应;对照组中,1例患者出现带状疱疹,2例患者出现尿路感染,3例患者发生胃肠道反应。观察组和对照组的不良反应的发生率比较差异无统计学意义($P>0.05$)。

3 讨论

系统性红斑狼疮是一种异质性自身免疫疾病,其发生主要和免疫因素和遗传因素有关^[7]。近年来,此病的发生率呈现出逐年增加的趋势,大部分患者存在重要脏器受损的情况,给患者生命安全带来严重威胁。系统性红斑狼疮患者的肝脏受损不但和免疫抑制剂、非甾类药物等药物的毒副作用有关,此病的本身也会导致局部免疫复合物沉着或血管炎进而导致肝脏受损^[8]。糖皮质激素是治疗系统性红斑狼疮较为常规的药物,吗替麦考酚酯分散片属于一种新型的免疫抑制剂,在抑制嘌呤代谢中主要是通过对次黄嘌呤核苷酸脱氢酶的阻碍来实现抑制的目的,阻碍细胞增生^[9,10]。已有研究者提出在治疗系统红斑狼疮患者中经吗替麦考酚酯分散片能产生显著的临床疗效^[11]。为探讨联合用药的优点,本研究对红斑狼疮患者予以糖皮质激素联合吗替麦考酚酯分散片进行治疗,研究结果显示:糖皮质激素联合吗替麦考酚酯分散片治疗系统性红斑狼疮的临床疗效高至92.86%,显著高于单纯糖皮质激素治疗者,究其原因可能主要是因为吗替麦考酚酯分散片可选择性的对B淋巴细胞和T淋巴细胞产生抑制作用,进而阻碍细胞免疫反应和机体体液免疫反应,并且能阻碍淋巴细胞和单核细胞浸润,直接对炎症反应发挥抑制作用。因此,吗替麦考酚酯分散片在免疫系统中发挥着较好的调节作用^[12-14]。

相关研究表明吗替麦考酚酯分散片可阻碍自身抗体的产生,进而发挥控制狼疮活动的功能,并且吗替麦考酚酯分散片可控制患者主要脏器的受损程度,并不会影响肝细胞、卵巢^[15]。本次研究结果显示:糖皮质激素联合吗替麦考酚酯分散片治疗的患者中,1例患者出现带状疱疹,1例患者发生尿路感染,2例患者出现胃肠道反应,其不良反应率较低,提示吗替麦考酚酯分散片并不会对重要脏器功能造成严重影响,也不会因为药物的增加而加大不良反应率,表明吗替麦考酚酯分散片具有较高的安全性。

相关研究表明系统性红斑狼疮患者体内中的B淋巴细胞会刺激因子基因表达水平,B淋巴细胞刺激因子的浓度水平较高^[16,17]。B淋巴细胞刺激因子作为细胞共刺激分子,会对免疫细胞的激活过程起着参与性作用,特别是能有效调节B细胞的激活、分化及增殖,导致机体免疫系统尤其是体内中的多种自身抗原成分,会有相应的自身抗体产生,进而升高多种免疫球蛋白浓度^[18-20]。已有研究者提出在系统性红斑狼疮患者中,IgA、IgG、IgM、CRP、ESR水平较高,提示体液免疫紊乱是系统性红斑狼疮发病的主要因素,当致病因子流入人体后,会导致Th细胞产生一系列的细胞因子,进而活化B细胞产生大量的抗体^[21-23],抗原和抗体结合形成会有大量的免疫复合物产生,在血管壁、关节滑膜处沉积,激活补体,发生一系列免疫紊乱,损伤组织,并且上述指标升高的幅度和患者病程的严重程度存在密切关联性^[24-26]。

本次研究结果显示:在系统性红斑狼疮患者治疗前,其IgA、IgG、IgM、CRP、ESR水平较高,究其原因主要是因为系统性红斑狼疮是一种免疫性疾病,主要表现为多系统受损且存在多种自身抗体,患者外周血淋巴细胞在活动期的凋亡速度会迅速提升,细胞凋亡后所产生的抗原成分会对机体产生自身抗体造成刺激性影响,相应的抗原和抗体结合后会有抗原抗体免疫复合物形成,进而激活补体系统,导致补体成分的消耗^[27-30]。而糖皮质激素联合吗替麦考酚酯分散片治疗后,患者的IgA、IgG、IgM、CRP、ESR水平显著降低,提示两种药物联合使用更能有效改善患者紊乱的免疫系统。

综上所述,糖皮质激素联合吗替麦考酚酯分散片能有效改善系统性红斑狼疮患者的免疫功能,临床疗效良好,安全性高。

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