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艾拉莫德联合沙利度胺对强直性脊柱炎患者免疫球蛋白及 ESR、C3、C4 的影响 *

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摘要 目的：探讨艾拉莫德联合沙利度胺对强直性脊柱炎患者免疫球蛋白及血沉（ESR）、补体 C3（C3）、补体 C4（C4）的影响。**方法：**选择 2016 年 11 月到 2019 年 12 月在我院接受治疗的 149 例强直性脊柱炎患者，采用随机数表法分为联合组（n=75）和单药组（n=74）。单药组给予沙利度胺治疗，联合组在单药组的基础上给予艾拉莫德治疗。比较两组临床疗效、免疫球蛋白、ESR、C3、C4、肿瘤坏死因子（TNF-α）、C 反应蛋白（CRP）、临床症状情况及不良反应发生情况。**结果：**治疗后，两组总有效率比较差异显著（P<0.05）；与治疗前比较，联合组和单药组免疫球蛋白水平检验结果比较无显著差异；治疗后，联合组和单药组 IgA、IgG 及 IgM 水平均随着时间的推移而下降，且联合组低于单药组，差异显著（P<0.05）；与治疗前比较，联合组和单药组 ESR、C3、C4 水平检验结果比较无显著差异；治疗后，联合组和单药组 ESR、C3 及 C4 水平均随着时间的推移而下降，且联合组低于单药组，差异显著（P<0.05）；与治疗前比较，联合组和单药组炎症因子水平检验结果比较无显著差异；治疗后，联合组和单药组 TNF-α、CRP 水平均随着时间的推移而下降，且联合组低于单药组，差异显著（P<0.05）；与治疗前比较，联合组和单药组临床症状比较无显著差异；治疗后，联合组和单药组关节肿胀、晨僵时间均随着时间的推移而下降，且联合组低于单药组，差异显著（P<0.05）；联合组与单药组患者不良反应总发生率相比，差异无统计学意义（P>0.05）。**结论：**在强直性脊柱炎患者中应用艾拉莫德联合沙利度胺效果显著，可有效改善患者免疫球蛋白及 ESR、C3、C4 水平，且不增加不良反应。

关键词：艾拉莫德；沙利度胺；强直性脊柱炎；免疫球蛋白；补体 C3；补体 C4

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Effects of Elamud Combined with Thalidomide on Immunoglobulin, ESR, C3 and C4 in Patients with Ankylosing Spondylitis*

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ABSTRACT Objective: To study Effects of elamud combined with thalidomide on immunoglobulin, ESR, C3 and C4 in patients with ankylosing spondylitis. **Methods:** 149 patients with ankylosing spondylitis treated in our hospital from November 2016 to December 2019 were selected and divided into the combined group (n=75) and the single drug group (n=74) by random number table method. The monotherapy group was given thalidomide treatment, and the combination group was given Alamodern treatment on the basis of the control group. The clinical efficacy, immunoglobulin, ESR, C3, C4, tumor necrosis factor (TNF-α), C-reactive protein (CRP), clinical symptoms and adverse reactions of the two groups were compared. **Results:** After treatment, the total effective rate of the two groups was significantly different (P<0.05). There was no significant difference in immunoglobulin levels between the combination group and the single drug group compared with that before treatment. After treatment, IgA, IgG and IgM levels in the combined group and the control group all decreased with the passage of time, and the levels in the combined group were lower than those in the control group, with significant differences (P<0.05). There was no significant difference in ESR, C3 and C4 levels between the combined group and the single drug group compared with that before treatment. After treatment, ESR, C3 and C4 levels in both the combined group and the control group decreased with the passage of time, and the levels in the combined group were lower than those in the control group, with significant differences (P<0.05). There was no significant difference in inflammatory factor levels between the combined group and the monotherapy group compared with the pre-treatment group. After treatment, the levels of TNF-α and CRP in both the combined group and the control group decreased over time, and the levels of TNF- and CRP in the combined group were lower than those in the control group, with significant differences(P<0.05). There was no significant difference in clinical symptoms between the combination group and the single drug group compared with the pre-treatment group. After treatment, the time of joint swelling and morning stiffness in the combined group and the control group decreased with the passage of time, and the difference was significant (P<0.05). There was no statistically significant

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difference in the total incidence of adverse reactions between the combined group and the single drug group (P>0.05). **Conclusion:** In patients with ankylosing spondylitis, the application of elamodt combined with thalidomide has a significant effect, which can effectively improve the immunoglobulin and ESR, C3 and C4 levels in patients without increasing adverse reactions.

Key words: Elamud; Thalidomide; Ankylosing spondylitis; Immunoglobulin; C3. Complement C4

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前言

强直性脊柱炎是较为常见的慢性进行性脊柱关节病,属于自身免疫性疾病,多发生于青少年,主要累及中轴骨关节,早期部分患者仅表现为轻微腰背发僵、肌肉疼痛等,可误诊为纤维肌痛综合征,易导致病情延误,失去最佳治疗时机[1,2]。近年来,多项研究发现免疫球蛋白及 ESR、C3、C4 介导了强直性脊柱炎的发展[3-5]。免疫球蛋白是机体重要的免疫系统,在多种免疫性疾病中表达异常[6]。ESR 是强直性脊柱炎患者常规检查指标,在该病中呈高表达,能准确反映出患者体内存在炎症反应[7]。补体是血清中具有酶活性的一组球蛋白, 参与了适应性调节免疫, C3、C4 是是补体的成分,能清除免疫复合物,调节免疫作用[8]。

沙利度胺是治疗强直性脊柱炎的常用药物,可抑制血管新生,改善机体免疫调节功能;艾拉莫德一种新型抗风湿药物,调节免疫反应的同时抑制各种炎症细胞因子,目前已有部分研究将其用于强直性脊柱炎的治疗中[9,10]。但关于艾拉莫德联合沙利度胺对强直性脊柱炎的研究还需进一步探讨。因此,本研究将艾拉莫德联合沙利度胺用于强直性脊柱炎的治疗中,并分析联合用药对患者免疫球蛋白及 ESR、C3、C4 的影响。

1 资料与方法

1.1 一般资料

选择 2016 年 11 月到 2019 年 12 月在我院接受治疗的 149 例强直性脊柱炎患者,研究已获得我院伦理委员会批准实施。采用随机数表法分为 2 组,联合组 75 例,其中男 56 例,女 19 例,年龄 22~36 岁,平均(28.56± 2.13)岁,病程 2~11 月,平均(7.52± 1.21)月;单药组 74 例,其中男 59 例,女 15 例,年龄 21~39 岁,平均(28.62± 2.21)岁,病程 2~10 月,平均(7.47± 1.23)月。两组基线资料无明显差异,可比较。

纳入标准:① 参照《强直性脊柱炎的诊断与治疗骨科专家共识》[11]确诊;② 临床病史、症状、实验室指标及影像学检查确诊为强直性脊柱炎;③ 心脑肾等器官无明显障碍;④ 未接受抗肿瘤坏死因子药物治疗;⑤ 签署知情同意书。排除标准:① 近期接受过正规免疫调节剂治疗;② 沟通障碍者;③ 肝脏血管畸形、血管瘤等疾者;④ 日常生活能力丧失,完全依赖;⑤ 无法言语交流者;⑥ 依从性较差者;⑦ 凝血功能障碍及血液系统病变者。

1.2 方法

单药组给予沙利度胺治疗:沙利度胺(规格:25 mg,生产厂家:常州制药厂有限公司,国药准字:H32026129)25 mg/ 次,1 d 2 次。联合组在单药组的基础上给予艾拉莫德治疗:艾拉莫德(规格:25 mg, 生产厂家: 先声药业有限公司, 国药准字:H20110084)25 mg/ 次,1 d 2 次。

1.3 观察指标

采集肘静脉血 4 mL,提取血清,采用双抗体夹心酶联免疫吸附法测定 TNF-α、CRP; 记录免疫球蛋白、ESR、C3 及 C4、关节肿胀、晨僵时间及不良反应发生情况。

疗效评定标准:显效:疼痛、肿胀症状消失、血沉降低;有效:疼痛、肿胀症状消失、血沉降低不明显;无效:无明显改善或加重。

1.4 统计学分析

以 spss18.0 软件包处理,符合正态分布计量资料用均数± 标准差($\bar{x}\pm s$)表示,组间比较使用独立样本 t 检验,计数资料以率表示,x^2 检验,P<0.05 表示差异具有统计学意义。

2 结果

2.1 联合组与单药组临床疗效对比

治疗后,两组总有效率比较差异显著(P<0.05)见表 1。

表 1 联合组与单药组临床疗效对比[n(%)]

Table 1 Comparison of clinical efficacy between combined group and single drug group[n(%)]

Groups	n	Excellent	valid	Invalid	Total effective rate
Joint group	75	36(48.00)	29(38.67)	10(13.33)	65(86.6)
Single drug group	74	29(39.18)	16(21.62)	29(39.19)	45(60.81)
x^2 value					12.887
P value					0.000

2.2 联合组与单药组免疫球蛋白含量对比

与治疗前比较,联合组和单药组免疫球蛋白水平检验结果比较无显著差异;治疗后,联合组和单药组 IgA、IgG 及 IgM 水平均随着时间的推移而下降,且联合组低于单药组,差异显著(P<0.05),见表 2。

2.3 联合组与单药组 ESR、C3、C4 含量对比

与治疗前比较, 联合组和单药组 ESR、C3、C4 水平检验结果比较无显著差异;治疗后,联合组和单药组 ESR、C3 及 C4 水平均随着时间的推移而下降,且联合组低于单药组,差异显著(P<0.05),见表 3。

表 2 联合组与单药组免疫球蛋白含量对比($\bar{x}\pm s$,g/L)

Table 2 Comparison of immunoglobulin content between the combined group and the single drug group($\bar{x}\pm s$, g/L)

Groups	n	IgA		IgG		IgM	
		Before the treatment	After treatment	Before the treatment	After treatment	Before the treatment	After treatment
Joint group	75	2.79± 1.21	2.31± 0.89	13.65± 4.12	7.56± 2.31	2.21± 0.61	1.14± 0.23
Single drug group	74	2.81± 1.22	2.65± 0.96	13.71± 4.21	10.12± 2.35	2.19± 0.63	1.65± 0.35
t value		0.100	2.242	0.088	6.706	0.197	10.525
P value		0.920	0.026	0.930	0.000	0.844	0.000

表 3 联合组与单药组 ESR、C3、C4 含量对比($\bar{x}\pm s$)

Table 3 Comparison of ESR, C3 and C4 in the combined group and the single drug group($\bar{x}\pm s$)

Groups	n	ESR(mm/h)		C3(g/L)		C4(g/L)	
		Before the treatment	After treatment	Before the treatment	After treatment	Before the treatment	After treatment
Joint group	75	55.21± 15.71	8.73± 2.34	1.45± 0.31	1.21± 0.32	0.45± 0.21	0.38± 0.11
Single drug group	74	55.08± 15.72	15.46± 3.68	1.46± 0.28	1.35± 0.33	0.46± 0.22	0.43± 0.18
t value		0.050	13.339	0.207	2.629	0.284	2.049
P value		0.959	0.000	0.837	0.009	0.777	0.042

2.4 联合组与单药组炎症因子含量对比

与治疗前比较,联合组和单药组炎症因子水平检验结果比较无显著差异;治疗后,联合组和单药组 TNF-α、CRP 水平均随着时间的推移而下降,且联合组低于单药组,差异显著(P<0.05),见表 4。

表 4 联合组与单药组炎症因子含量对比($\bar{x}\pm s$)

Table 4 Comparison of inflammatory factors between the combined group and the single drug group($\bar{x}\pm s$)

Groups	n	TNF-α(pg/mL)		CRP(mg/L)	
		Before the treatment	After treatment	Before the treatment	After treatment
Joint group	75	18.97± 3.63	6.71± 0.95	50.31± 8.97	10.21± 2.12
Single drug group	74	19.02± 3.68	10.58± 1.68	50.25± 9.03	17.51± 3.84
t value		0.083	17.337	0.041	14.391
P value		0.934	0.000	0.968	0.000

2.5 联合组与单药组临床症状情况对比

与治疗前比较,联合组和单药组临床症状比较无显著差异;治疗后,联合组和单药组关节肿胀、晨僵时间均随着时间的推移而下降,且联合组低于单药组,差异显著(P<0.05),见表 5。

表 5 联合组与单药组临床症状情况对比($\bar{x}\pm s$)

Table 5 Comparison of clinical symptoms between the combined group and the single drug group($\bar{x}\pm s$)

Groups	n	Joint swelling(mm)		Morning stiffness time(min)	
		Before the treatment	After treatment	Before the treatment	After treatment
Joint group	75	17.23± 5.31	7.41± 1.25	44.85± 14.75	17.45± 3.21
Single drug group	74	17.31± 5.43	10.46± 2.34	44.79± 14.81	24.18± 5.82
t value		0.091	9.942	0.025	8.755
P value		0.928	0.000	0.980	0.000

2.6 联合组与单药组不良反应对比

联合组与单药组患者不良反应总发生率相比,差异无统计学意义(P>0.05),见表 6。

3 讨论

强直性脊柱炎是以骶髂关节、脊柱附着点炎症反应为特征

表 6 联合组与单药组不良反应对比[n(%)]

Table 6 Comparison of adverse reactions between the combined group and the single drug group[n(%)]

Groups	n	The rash	Respiratory infection	swelling	drowsiness	The total incidence of
Joint group	75	1	1	0	1	3(4.00)
Single drug group	74	2	0	2	1	5(6.76)
x^2 value						0.557
P value						0.455

疾病,具有致残率高等特点,其发病机制尚不明确,主要以椎间盘纤维化或骨性强直，随着病情的进展可引起心肺等功能下降,严重者可致残,严重影响患者的日常生活[12-14]。其发病机制较为复杂,可能与遗传、感染、免疫功能异常等危险因素有关。有研究显示,强直性脊柱炎死亡病理演变过程为韧带附着部位出现炎性病变,经反应性吸收后形成骨化,导致脊柱或受累关节骨性强直,造成椎体出现竹节样变化,最终引起其他局部骨化[15,16]。因此,对患者给予早期治疗对患者具有重要意义。

目前对于强直性脊柱炎尚无确切的根治方法,仅以运动和药物治疗,缓解患者临床症状,控制病情进展为主,沙利度胺是一种合成性谷氨酸衍生物,能抑制血管生成、刺激免疫系统活性,同时具有较强的抗炎作用,被广泛用于免疫性疾病的治疗中[17-19]。有研究显示,沙利度胺可有效改善强直性脊柱炎患者的中轴关节及外周关节[20]。但有学者认为沙利度胺单独用于治疗强直性脊柱炎效果单一,需联合其他药物共同治疗,提高临床疗效[21]。艾拉莫德是一种新型小分子药物,近几年被使用用于治疗类风湿关节炎,能抑制炎性因子的释放及炎症反应中缓激肽增加 [22]。有研究显示，艾拉莫德主要活性成分为 T-614,而 T-614 是一种选择性抑制 COX-2 化合物,具有类似非甾体止痛药的作用,同时可以明显减少外周血 IgM 的产生,抑制多种炎症细胞的生成,降低免疫球蛋白[23,24]。艾拉莫德是一种新型抗风湿药物,被临床广泛用于治疗类风湿性关节炎,且取得不错的效果,但目前国内外关于艾拉莫德用于治疗强直性脊柱炎的相关报道较少[25]。因此本研究将艾拉莫德联合沙利度胺于与单独使用沙利度胺治疗强直性脊柱炎进行对比,结果显示,联合治疗的患者总有效率明显高于单独使用沙利度胺的患者，提示,艾拉莫德联合沙利度胺可提高强直性脊柱炎的临床疗效,且治疗期间两组患者均为发生明显不良反应,说明,联合治疗具有较高的安全性,不会增加药物不良反应的发生。Gamayunova K A[26]等研究也显示,艾拉莫德对能改善强直性脊柱炎患者外周关节炎症,且见效较快。

免疫球蛋白是机体血清主要的抗体成分,它的缺乏和增高多见于各种先天性及免疫缺陷综合征，其中 IgA、IgG 及 IgM 是对人体免疫功能起重要作用的免疫抗体,而强直性脊柱炎是一种慢性自身免疫性疾病,当疾病发生时伴有不同程度的免疫功能紊乱[27,28]。IgA 是参与黏膜局部免疫的主要抗体,分血清型和分泌型，血清性 IgA 是维持机体内环境稳定有益的免疫效应;分泌型 IgA 性能稳定,能阻挡病原体及有害抗原进入体内,构成黏膜第一线防御机制，能反映强直性脊柱炎的疾病活动,当患者病情加重时，其含量增加;IgG 是机体再次免疫应答的抗体,是存留时间最长的一种免疫球蛋白,具有吞噬调理作用,能够反映机体免疫的水平;IgM 是个体发育中最早出现合成和分泌的抗体,含量低,半衰期短,且没有独立的吞噬调理作用。有研究显示,IgA、IgG 及 IgM 在强直性脊柱炎患者中表达较高,说明,患者体内存在体液免疫亢进或一定程度的组织损伤。Wang H[29]等研究显示,当患者免疫球蛋白升高时主要以 IgA 升高最明显,且可随着疾病的严重程度而升高。补体是天然免疫系统的重要组成部分，具有生物学活性的补体片段的生成,调控炎症和免疫反应的作用,C3、C4 是补体的两组，当发生急性炎症时其含量增加。本研究将艾拉莫德联合沙利度胺用于治疗强直性脊柱炎,并观察患者免疫球蛋白水平及 C3、C4 变化,结果显示，联合治疗的患者 IgA、IgG、IgM 及 C3、C4 水平明显降低,提示,联合治疗能明显降低患者免疫球蛋白水平及补体,促进患者恢复。有研究显示,多种炎症因子参与了强直性脊柱炎的发展[30]。ESR 在正常情况下处于狭窄范围,在病理情况下其速度明显增快,其水平升高在一定程度上反映炎症状态,可作为评估有无活动性病变的指标。TNF-α、CRP 是常见的严重因子,参与了多种炎症疾病的发生,本研究结果显示,治疗后患者 ESR、TNF-α、CRP、及关节肿胀、晨僵时间均明显下降,且联合治疗的患者下降程度优于单药组,进一步说明了艾拉莫德联合沙利度胺能通过降低患者炎症反应，改善患者临床症状。Dubash S[30]等研究也显示,在强直性脊柱炎患者使用艾拉莫德 3 个月后患者免疫球蛋白及 TNF-α 明显下降，与本研究结果相似。

综上所述,艾拉莫德联合沙利度胺能明显降低强直性脊柱炎患者免疫球蛋白及 ESR、C3、C4 水平,临床疗效较高。

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