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特布他林联合羧甲司坦片治疗慢性阻塞性肺疾病的疗效及对血清MMP-9、MMP-12、TIMP-1的影响*

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摘要 目的：研究特布他林联合羧甲司坦片治疗慢性阻塞性肺疾病的疗效及对血清基质金属蛋白酶-9(MMP-9)、基质金属蛋白酶-12(MMP-12)、组织型金属蛋白酶抑制物(TIMP-1)水平的影响。**方法：**选取2015年3月至2018年2月我院收治的170例COPD患者，根据随机数字法分为观察组(87例)和对照组(83例)。对照组使用特布他林，观察组联合使用羧甲司坦。比较两组患者的临床疗效，治疗前后血清MMP-9、MMP-12、TIMP-1水平，肺功能指标，炎性因子水平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)，血清MMP-9、MMP-12、TIMP-1水平显著低于对照组(P<0.05)，最大呼气流速(PEF)、1秒用力呼气容积(FEV1)、用力肺活量(FVC)及FEV1/FVC显著高于对照组(P<0.05)，血清肿瘤坏死因子-α(TNF-α)、白细胞介素-8(IL-8)、中性粒细胞弹性蛋白酶(NE)水平均显著低于对照组(P<0.05)。观察组和对照组不良反应的发生率比较无显著差异(P>0.05)。**结论：**特布他林联合羧甲司坦片治疗COPD的临床疗效显著优于单用特布他林，且安全性更高，可能与其能有效降低血清MMP-9、MMP-12、TIMP-1水平有关。

关键词：特布他林；羧甲司坦片；慢性阻塞性肺疾病；基质金属蛋白酶-9；基质金属蛋白酶-12；组织型金属蛋白酶抑制物

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Efficacy of Terbutaline Combined with Carboxymethacetin Tablets in the Treatment of Chronic Obstructive Pulmonary Disease and Its Effect on the Serum MMP-9, MMP-12 and TIMP-1*

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ABSTRACT Objective: To study the efficacy of terbutaline combined with carboxymethine tablets in the treatment of chronic obstructive pulmonary disease and serum levels of matrix metalloproteinase-9 (MMP-9), matrix metalloproteinase-12 (MMP-12), tissue effect of type metalloproteinase inhibitor (TIMP-1). **Methods:** A total of 170 patients with COPD admitted in our hospital from March 2015 to February 2018 were enrolled, they were diveided into the observation group (87 patients) and the control group (83 patients) according to random number method. Terbutaline was used in the control group, and observation group combined with carboxymethylstatin. The clinical efficacy, serum levels of MMP-9, MMP-12 and TIMP-1 before and after treatment, lung function indicators, changes of inflammatory factors and occurrence of adverse reactions were compared between the two groups. **Results:** After treatment, the total clinical effective rate of the observation group was significantly higher than that of the control group (P<0.05). the serum MMP-9, MMP-12 and TIMP-1 levels in the observation group were significantly lower than the control group (P<0.05). the observation group with the ratios of PEF, FEV1, FVC and FEV1/FVC were significantly higher than those of the control group (P<0.05). The Serum of levels TNF-α, IL-8 and NE in the observation group were significantly lower than those in the control group (P<0.05). There was no significant difference in the incidence of adverse reaction between the observation group and the control group (P>0.05). **Conclusion:** The clinical efficacy of terbutaline combined with carboxymethylsteine tablets in the treatment of COPD is significantly better than that of terbutaline alone, and its safety is higher, which may be related to its effective reduction of serum levels of MMP-9, MMP-12 and TIMP-1.

Key words: Terbutaline; Carbostatin tablets; Chronic obstructive pulmonary disease; Matrix metalloproteinase-9; Matrix metalloproteinase-12; Tissue metalloproteinase inhibitor

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前言

慢性阻塞性肺疾病 (COPD) 属于呼吸系统常见的慢性疾病,发病率和死亡率均较高,给患者生活造成不良影响[1]。既往研究表明 COPD 的发生主要和营养不良、自主神经系统功能紊乱、氧化应激机制、抗蛋白酶和蛋白酶不平衡、炎症机制等因素有关。COPD 气道重塑的主要病理症状表现为肺泡腔变大、肺泡壁变薄、细支气管平滑肌增生、气道壁纤维化[2]。而肺气肿发生发展过程很大程度上和支气管肺泡组织中弹性成分降解有关。在维持肺功能和肺泡结构中,细胞外基质(ECM)降解与合成的平衡发挥着极其重要的作用。其中, 基质金属蛋白酶(MMPs)属于结构相似并能降解 ECM,在维持血管形成、细胞信号传导、组织细胞分化、正常组织结构等病理生理过程中发挥着极其重要的作用[3]。

特布他林作为 β2 受体特异性激动剂,能松弛气道平滑肌,阻碍中性粒细胞和肥大细胞所释放的炎性因子[4]。羧甲司坦属于呼吸系统常见的粘液溶解药物,能有效稀释炎症导致的分泌物,抗炎抗氧化作用较为显著[5]。为给临床治疗 COPD 方面提供更多的参考依据,本研究主要探讨了特布他林联合羧甲司坦片治疗慢性阻塞性肺疾病的疗效及对血清 MMP-9、MMP-12、组织型金属蛋白酶抑制物(TIMP-1)水平的影响,结果报道如下。

1 资料与方法

1.1 临床资料

选取 2015 年 3 月至 2018 年 2 月我院收治的 170 例 COPD 患者,纳入标准:① 符合《慢性阻塞性肺疾病全球倡议慢性阻塞性肺疾病指南》[6]中的标准;② 在加入本次研究前停止短效支气管扩张剂 24 h,长效支气管扩张剂 48 h;③ 近 1 个月内未出现 COPD 加重。排除标准:① 严重青光眼及心脑血管疾病者;② 风湿结缔组织疾病者;③ 急性肺栓塞;④ 恶性肿瘤疾病者。本研究已获得我院伦理委员会批准实施,同时患者及家属签署知情同意书。根据随机数字法分为观察组(87 例)和对照组(83 例)。观察组中,男性 51 例,女性 36 例;年龄为 56~74 岁,平均(65.43± 2.82)岁;病程为 3~12 年,平均(7.54± 1.32)年;肺功能分级:54 例 II 级,33 例 III 级;49 例有吸烟史。对照组中,男性 48 例,女性 35 例;年龄为 53~73 岁,平均(63.27± 2.91)岁;病程为 4~14 年,平均(7.61± 1.41)年;肺功能分级:52 例 II 级,31 例 III 级;46 例有吸烟史。两组患者的性别、年龄、病程、肺功能分级方面比较无显著差异(P>0.05),具有可比性。

1.2 治疗方法

所有患者均通过肾上腺素受体激动剂抗胆碱药、止咳化痰、氨茶碱、抗感染、吸氧等常规治疗,若伴有心力衰竭,可予以扩血管、利尿、强心治疗。对照组使用特布他林(生产厂家:阿斯利康制药有限公司,规格:50 mg,生产批号:20150114)治疗,雾化吸入,1.25 mg/ 次,2 次 / 天。观察组在对照组基础上使用羧甲司坦(生产厂家:广东台城制药股份有限公司,规格:0.25g*50 片,生产批号:20150211)治疗,口服,2 片 / 次,3 次 / 天。所有患者均需治疗 3 个月。

1.3 观察指标

评价两组患者的临床疗效,肺部体征、肺影像学、临床症状均恢复则为显效;肺部体征、肺影像学、临床症状中单项有所好转则为改善;临床症状未获得变化甚至加重则为无效。总有效 = 显效 + 改善。

在治疗前和治疗 3 个月后, 抽取患者 5 mL 静脉血, 转速 2000 r/min,离心 15 min,提取上清液,使用酶联免疫吸附法检测血清 MMP-9、MMP-12、TIMP-1、肿瘤坏死因子 -α(TNF-α)、白细胞介素 -8(IL-8)、中性粒细胞弹性蛋白酶(NE),上海酶联生物技术有限公司提供试剂盒,根据说明书完成本次操作。分析患者肺功能指标,用肺功能仪检测最大呼气流速(PEF)、1 秒用力呼气容积(FEV1)、用力肺活量(FVC)及 FEV1/FVC 比值。记录患者不良反应的发生情况。

1.4 统计学处理

选择 spss11.5 软件包处理本次实验数据, 计量资料用均数± 标准差($\bar{x}$± s)表示,组间比较行 t 检验,计数资料用[n(%)]表示,组间比较行 x^2 检验,以 P<0.05 表明差异有统计学意义。

2 结果

2.1 两组临床疗效的比较

治疗后,观察组临床总有效率显著高于对照组(93.11% vs. 78.31%,P<0.05),见表 1。

表 1 两组临床疗效的比较[n(%)]

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

Groups	Excellent	To improve the	Invalid	Total effective rate
Observation group(n=87)	64(73.56)	17(19.54)	6(6.89)	81(93.11)
Control group(n=83)	37(44.58)	28(33.73)	18(21.69)	65(78.31)
u/x^2 value		u=3.967		x^2=7.664
P value		P=0.000		P=0.006

2.2 两组患者治疗前后血清 MMP-9、MMP-12、TIMP-1 水平的变化比较

治疗前, 两组患者血清 MMP-9、MMP-12、TIMP-1 水平比较无显著差异 (P>0.05); 治疗后, 两组患者血清 MMP-9、MMP-12、TIMP-1 水平较治疗前均显著降低(P<0.05),且观察组的血清 MMP-9、MMP-12、TIMP-1 水平均显著低于对照组(P<0.05),见表 2。

表 2 两组患者治疗前后血清 MMP-9、MMP-12、TIMP-1 水平的变化比较($\bar{x}\pm s$)

Table 2 Comparison of the changes of serum MMP-9, MMP-12, TIMP-1 levels between two groups before and after treatment($\bar{x}\pm s$)

Groups	MMP-9(ng/mL)		MMP-12(ng/mL)		TIMP(ng/mL)	
	Before the treatment	After treatment	Before the treatment	After treatment	Before the treatment	After treatment
Observation group(n=87)	5.12± 0.52	1.12± 0.15	5.92± 0.63	0.98± 0.07	3.89± 0.41	0.87± 0.05
Control group(n=83)	5.08± 0.49	3.48± 0.38	6.01± 0.65	3.21± 0.37	3.94± 0.43	1.53± 0.14
t value	0.516	53.713	0.917	55.198	0.776	41.302
P value	0.607	0.000	0.361	0.000	0.439	0.000

2.3 两组患者治疗前后肺功能的变化比较

治疗前，两组患者 PEF、FEV1、FVC、FEV1/FVC 比值比较无显著差异 (P>0.05)；治疗后，两组患者 PEF、FEV1、FVC、FEV1/FVC 比值均显著高于治疗前，且观察组以上指标均显著高于对照组(P<0.05)，见表 3。

表 3 两组患者治疗前后肺功能指标的变化比较($\bar{x}\pm s$)

Table 3 Comparison of the changes of of pulmonary function index between two groups before and after treatment($\bar{x}\pm s$)

Groups	PEF(L/s)		FEV1(L)		FVC(V/L)		FEV1/FVC(%)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group(n=87)	2.05± 0.27	2.98± 0.31	36.16± 3.13	44.97± 5.24	1.12± 0.11	1.81± 0.22	51.24± 5.12	59.43± 5.43
Control group (n=83)	2.07± 0.26	2.52± 0.28	37.15± 3.12	41.54± 4.18	1.15± 0.12	1.52± 0.15	52.02± 5.18	55.32± 5.25
t value	0.492	10.137	2.065	4.704	1.700	9.995	0.987	5.014
P value	0.624	0.000	0.041	0.000	0.091	0.000	0.325	0.000

2.4 两组患者治疗前后血清炎性因子水平的变化比较

治疗前，两组患者血清 TNF-α、IL-8、NE 水平比较无显著差异(P>0.05)，治疗后，两组患者血清 TNF-α、IL-8、NE 水平均显著低于治疗前(P<0.05)，且观察组的血清 TNF-α、IL-8、NE 水平均显著低于对照组(P<0.05)，见表 4。

表 4 两组患者治疗前后血清炎性因子水平的变化比较($\bar{x}\pm s$)

Table 4 Comparison of the changes of serum inflammatory factors levels between two groups before and after treatment($\bar{x}\pm s$)

Groups	TNF-α(ng/L)		IL-8(pg/mL)		NE(μg/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group(n=87)	15.32± 1.54	5.43± 0.51	22.43± 2.15	7.43± 0.72	78.43± 7.98	61.24± 5.43
Control group(n=83)	15.41± 1.52	9.54± 0.92	23.01± 2.17	15.92± 1.53	78.51± 7.92	71.40± 7.02
t value	0.383	36.242	1.750	46.632	0.066	10.583
P value	0.702	0.000	0.082	0.000	0.948	0.000

2.5 两组不良反应发生情况的比较

对照组发生乏力为 1 例，恶心 2 例，呕吐 2 例；观察组发生乏力 2 例，恶心 2 例，呕吐 3 例，观察组和对照组不良反应的发生率比较无显著差异(P>0.05)。

3 讨论

COPD 属于慢性气道疾病，表现为气流阻塞进行性发展，同时伴有不同程度上的肺气肿、小气道炎症、黏液腺增生、支气管炎症[7]。肺对气体或有毒颗粒的异常炎性反应通常表现为气流受限[8,9]。呼吸道及周围组织慢性炎症会导致呼吸道受损，改变呼吸道结构，主要表现为细胞外基质沉积过度，管腔狭窄纤维化，平滑肌增生[10,11]。COPD 不可逆性气流受限很大程度上和呼吸道细胞外基质重塑有关，主要是因为过量的蛋白酶而致的抗蛋白酶不平衡，最终破坏肺脏组织结构，扩大气腔[12,13]。COPD 的发病很大程度上和 MMP 有关，明胶酶 B-MMP-9 能降解肺泡壁的蛋白多糖、弹力纤维、胶原纤维等细胞外基质成分[14,15]。在调解细胞外基质降解合成中 MMP-9、MMP-12、TIMP-1 作为主要酶类，在正常肺组织中 MMP-9 并不会产生，当受到刺激时，内皮细胞、成纤维细胞、肺泡 II 型细胞、支气管上皮细胞等均会产生；MMP-12 也被称之为人巨噬细胞弹性蛋白酶，低密度脂蛋白、白介素 -4 等细胞因子均会刺激或诱导 MMP-12 在转录水平中的表达[16,17]。

特布他林作为β2受体特异性激动剂，可阻碍中性粒细胞和肥大细胞释放炎性介质，松弛气道平滑肌，缓解气道黏膜下水肿，有助于气道纤毛运动，从而能及时缓解及消除COPD症状[18-20]。COPD患者急性加重发作频率增加、肺功能下降、气流阻塞很大程度上和气道粘液高分泌有关，在COPD发病机制中最为重要的是氧化应激反应，羧甲司坦属于常见的祛痰药物，具有抗氧化、抗炎、祛痰等功效[21-24]。羧甲司坦懒氨酸盐作为羟自由基和次氯酸的有效清除剂，可诱导IL-8的释放，从而降低外周血多形核白细胞IL-8的合成，实现抗炎目的，并且能缓解自由基给肺造成的损伤，降低弹性蛋白酶和炎性细胞自由基的分泌，实现抗氧化、抗炎效应[25-27]。本研究结果显示特布他林联合羧甲司坦片治疗后，COPD患者患者的血清TNF-α、IL-8、NE、MMP-9、MMP-12、TIMP-1水平较单纯特布他林治疗均显著下降，提示加用羧甲司坦更能有效修复COPD患者气道，因此有助于患者肺功能的改善。羧甲司坦属于粘液调节剂，能增加低粘度的唾液黏蛋白分泌量，减少高粘度的岩藻黏蛋白，进而减少痰液粘滞性，有助于痰液咳出，同时可通过黏蛋白和羧甲基中二硫键的相互作用，有助于正常粘液粘弹性的恢复，提高粘膜纤毛清除率，从而改善患者临床症状[28-30]。两种治疗方案的不良反应率比较无显著差异，提示羧甲司坦并不会增加不良反应，安全性较高。

综上所述，特布他林联合羧甲司坦片治疗COPD的临床疗效显著优于单用特布他林，且安全性更高，可能与其能有效降低血清MMP-9、MMP-12、TIMP-1水平有关。

参 考 文 献(References)

[1] Liang J B, Liu L J, Fang Q H. Clinical characteristics of patients with chronic obstructive pulmonary disease overlapped with bronchial asthma [J]. Annals of Allergy Asthma & Immunology Official Publication of the American College of Allergy Asthma & Immunology, 2017, 118(5): 564-569

[2] Robalo N A, Tátá M. The impact of anaemia and iron deficiency in chronic obstructive pulmonary disease: A clinical overview [J]. Revista Portuguesa De Pneumologia, 2017, 23(3): 146-155

[3] Robalo N A, Tátá M. The impact of anaemia and iron deficiency in chronic obstructive pulmonary disease: A clinical overview [J]. Revista Portuguesa De Pneumologia, 2017, 23(3): 146-155

[4] Grochowalska A, Kozioå-Montewka M, Sobieszczaå Ska A. Analysis of Acinetobacter baumannii resistance patterns in patients with chronic obstructive pulmonary disease (COPD) in terms of choice of effective empiric antibiotic therapy [J]. Ann Agric Environ Med, 2017, 24(2): 307-311

[5] Joaquim Gea, Sergi Pascual, Carme Casadevall, et al. Muscle dysfunction in chronic obstructive pulmonary disease: update on causes and biological findings[J]. J Thorac Dis, 2015, 7(10): E418-E438

[6] Castillo A, Edriss H, Selvan K, et al. Characteristics of Patients With Congestive Heart Failure or Chronic Obstructive Pulmonary Disease Readmissions Within 30 Days Following an Acute Exacerbation[J]. Qual Manag Health Care, 2017, 26(3): 152-159

[7] Jinjuvadia C, Jinjuvadia R, Mandapakala C, et al. Trends in Outcomes, Financial Burden, and Mortality for Acute Exacerbation of Chronic Obstructive Pulmonary Disease (COPD) in the United States from 2002 to 2010 [J]. Copd Journal of Chronic Obstructive Pulmonary Disease, 2017, 14(1): 72-79

[8] Wouters E F M, Wouters B B R A F, Augustin I M L, et al. Personalized medicine and chronic obstructive pulmonary disease [J]. Current Opinion in Pulmonary Medicine, 2017, 23(3): 241-246

[9] Koul P A, Mir H, Akram S, et al. Respiratory viruses in acute exacerbations of chronic obstructive pulmonary disease[J]. Lung India Official Organ of Indian Chest Society, 2017, 34(1): 29-33

[10] Bajpai J, Prakash V, Kant S, et al. Study of oxidative stress biomarkers in chronic obstructive pulmonary disease and their correlation with disease severity in north Indian population cohort[J]. Lung India Official Organ of Indian Chest Society, 2017, 34(4): 324-329

[11] Dransfield M T, Kunisaki K M, Strand M J, et al. Acute Exacerbations and Lung Function Loss in Smokers with and without Chronic Obstructive Pulmonary Disease[J]. Am J Respir Crit Care Med, 2017, 195(3): 324-330

[12] Jatene T, Biering-SãRensen T, Nochioka K, et al. Frequency of Cardiac Death and Stent Thrombosis in Patients With Chronic Obstructive Pulmonary Disease Undergoing Percutaneous Coronary Intervention (from the BASKET-PROVE I and II Trials)[J]. American Journal of Cardiology, 2017, 119(1): 14-19

[13] Sehgal I S, Dhooria S, Agarwal R. Chronic obstructive pulmonary disease and malnutrition in developing countries [J]. Current Opinion in Pulmonary Medicine, 2017, 23(2): 139-148

[14] Ji Ye Jung, Dong Pil Choi, Sungho Won, et al. Relationship of Vitamin D Binding Protein Polymorphisms and Lung Function in Korean Chronic Obstructive Pulmonary Disease [J]. Yonsei Med J, 2014, 55 (5): 1318-1325

[15] Goudis C A. Chronic obstructive pulmonary disease and atrial fibrillation: An unknown relationship [J]. Journal of Cardiology, 2017, 69 (5): 699-705

[16] Li Y, Xie L, Xin S, et al. Values of procalcitonin and C-reactive proteins in the diagnosis and treatment of chronic obstructive pulmonary disease having concomitant bacterial infection[J]. Pakistan Journal of Medical Sciences, 2017, 33(3): 566-569

[17] Hwang S L, Lin Y C, Guo S E, et al. Fine particulate matter on hospital admissions for acute exacerbation of chronic obstructive pulmonary disease in southwestern Taiwan during 2006â2012 [J]. International Journal of Environmental Health Research, 2017, 27 (2): 95-105

[18] Hannu Kankaanranta, Terttu Harju, Maritta Kilpeläinen, et al. Diagnosis and Pharmacotherapy of Stable Chronic Obstructive Pulmonary Disease: The Finnish Guidelines [J]. Basic Clin Pharmacol Toxicol, 2015, 116(4): 291-307

[19] Jinkyeong Park, Ju Hee Song, Dong-Ah Park, et al. Systematic Review and Meta-Analysis of Pulmonary Hypertension Specific Therapy for Exercise Capacity in Chronic Obstructive Pulmonary Disease[J]. J Korean Med Sci, 2013, 28(8): 1200-1206

[20] Rohit Budhiraja, Tauseef A. Siddiqi, Stuart F. Quan. Sleep Disorders in Chronic Obstructive Pulmonary Disease: Etiology, Impact, and Management[J]. J Clin Sleep Med, 2015, 11(3): 259-270

[21] Palen J V D, Klein J J, Kerkhoff A H, et al. Evaluation of the effectiveness of four different inhalers in patients with chronic obstructive pulmonary disease[J]. Thorax, 2017, 50(11): 1183-1187

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(3): 239-244

[9] Wang RF, Milam PB, Chung C, et al. Successful treatment of inflammatory linear verrucous epidermal nevus (ILVEN) with 308-nm excimer laser: Patient patient required[J]. Photodermatol Photoimmunol Photomed, 2019, 35(3): 196-197

[10] 中国中西医结合学会皮肤性病专业委员会色素病学组. 白癜风临床分型及疗效标准(2003 年修定稿)[J]. 中国中西医结合皮肤性病学杂志, 2004, 3(1): 65

[11] 黄骏, 林福全, 洪为松, 等. 白癜风黑素细胞移植供皮区同形反应严重程度与疗效的关系 [J]. 中华皮肤科杂志, 2017, 50(10): 751-753

[12] Yi X, Guo W, Shi Q, et al. SIRT3-Dependent Mitochondrial Dynamics Remodeling Contributes to Oxidative Stress-Induced Melanocyte Degeneration in Vitiligo[J]. Theranostics, 2019, 9(6): 1614-1633

[13] Razmi TM, Kumaran SM, Parsad D. Trichloroacetic Acid 25% Peel to Facilitate Dermabrasion at Difficult Sites in Vitiligo Surgery [J]. Dermatol Surg, 2019, 45(5): 750-752

[14] Andrade SA, Baeta IGR, Ribeiro MM, et al. Mucosal vitiligo in angles of the mouth: clinical and fluorescence aspects [J]. Rev Assoc Med Bras (1992), 2019, 65(3): 330-332

[15] 法莹, 刘华绪. 308 nm 准分子激光联合他克莫司软膏治疗面部白癜风 656 例疗效评价 [J]. 中国麻风皮肤病杂志, 2016, 32(5): 281-283

[16] 刘哲, 曲生明, 巫毅, 等. 白癜风的免疫学发病机制及吡美莫司治疗白癜风的研究进展[J]. 中国老年学杂志, 2017, 37(10): 2588-2592

[17] 王静, 庞娟, 王博鹤, 等. 白癜风患儿抗核抗体、免疫球蛋白及补体检测的临床分析[J]. 现代生物医学进展, 2017, 17(2): 355-358

[18] 程芳. 白癜风的免疫学发病机制及治疗进展 [J]. 海南医学, 2018, 29(17): 2477-2479

[19] 魏伟, 何奕德, 李萌, 等. 调节性 T 细胞在白癜风发病机制中的作用及治疗应用[J]. 中国美容医学, 2018, 27(1): 133-136

[20] Hassan I, Bhat YJ, Majid S, et al. Association of Vitamin D Receptor Gene Polymorphisms and Serum 25-Hydroxy Vitamin D Levels inVitiligo-A Case-control Study [J]. Indian Dermatol Online J, 2019, 10 (2): 131-138

[21] Banerjee N, Gayen S, Modak D, et al. Systemic Redox Imbalance Along with Increased Serum Sialic Acid is Prevalent in Patients with ActiveVitiligo: A Study from a Tertiary Care Teaching Hospital of Eastern India[J]. Indian J Dermatol, 2019, 64(2): 97-100

[22] Rattanakaemakorn P, Phusuphitchayanan P, Pakornphadungsit K, et al. Efficacy and safety of 308-nm excimer lamp in the treatment of scalp psoriasis: a retrospective study [J]. Photodermatol Photoimmunol Photomed, 2019, 35(3): 172-177

[23] 薛慧. 糖皮质激素及他克莫司软膏联用 308nm 准分子激光治疗儿童及青少年白癜风的临床观察 [J]. 山西医药杂志, 2018, 47(5): 567-569

[24] Li L, Liang Y, Hong J, et al. The effectiveness of topical therapy combined with 308-nm excimer laser on vitiligo compared to excimer laser monotherapy in pediatric patients[J]. Pediatr Dermatol, 2019, 36 (1): e53-e55

[25] Wen X, Hamblin MR, Xian Y, et al. A preliminary study of fractional CO_2 laser added to topical tacrolimus combined with 308 nm excimer lamp for refractory vitiligo[J]. Dermatol Ther, 2019, 32(1): e12747

[26] 王春又, 游弋, 葛兰, 等. 白癜风免疫发病机制的研究进展[J]. 医学综述, 2017, 23(18): 3638-3641, 3646

[27] Wang LM, Zhang B, Li JJ, et al. The expression change of RORγt, BATF, and IL-17 in Chinese vitiligo patients with 308nanometers excimer laser treatment[J]. Dermatol Ther, 2018, 31(3): e12598

[28] Sushama S, Dixit N, Gautam RK, et al. Cytokine profile (IL-2, IL-6,? IL-17, IL-22, and TNF-α) in vitiligo-New insight into pathogenesis of disease[J]. J Cosmet Dermatol, 2019, 18(1): 337-341

[29] Bagherani N. The efficacy of 308 nm UV excimer light as monotherapy and combination therapy with topical khellin 4% and/or tacrolimus 0.1% in the treatment of vitiligo [J]. Dermatol Ther, 2016, 29(2): 137-138

[30] Sun Y, Wu Y, Xiao B, et al. Treatment of 308-nm excimer laser on vitiligo: A systemic review of randomized controlled trials [J]. J Dermatolog Treat, 2015, 26(4): 347-353

(上接第 535 页)

[22] Hobbs B D, Jong K D, Lamontagne M, et al. Genetic loci associated with chronic obstructive pulmonary disease overlap with loci for lung function and pulmonary fibrosis [J]. Nature Genetics, 2017, 49(3): 426-432

[23] Houben-Wilke S, JāRres R A, Bals R, et al. Peripheral Artery Disease and Its Clinical Relevance in Patients with Chronic Obstructive Pulmonary Disease in the COPD and Systemic Consequences-Comorbidities Network Study[J]. Am J Respir Crit Care Med, 2017, 195(2): 189-197

[24] Fowdar K, Chen H, He Z, et al. The effect of N-acetylcysteine on exacerbations of chronic obstructive pulmonary disease: A meta-analysis and systematic review [J]. Heart & Lung the Journal of Critical Care, 2017, 46(2): 120-128

[25] Singh S, Verma S K, Kumar S, et al. Evaluation of Oxidative Stress and Antioxidant Status in Chronic Obstructive Pulmonary Disease[J]. Scandinavian Journal of Immunology, 2017, 85(2): 130-137

[26] Hogg J C, Paré P D, Hackett T L. The Contribution of Small Airway Obstruction to the Pathogenesis of Chronic Obstructive Pulmonary Disease[J]. Physiological Reviews, 2017, 97(2): 529-552

[27] Sulaiman I, Cushen B, Greene G, et al. Objective Assessment of Adherence to Inhalers by Patients with Chronic Obstructive Pulmonary Disease[J]. Am J Respir Crit Care Med, 2017, 195(10): 1333-1343

[28] Mirza S, Benzo R. Chronic Obstructive Pulmonary Disease Phenotypes: Implications for Care [J]. Mayo Clinic Proceedings, 2017, 92 (7): 1104-1112

[29] Xiao B, Wang M, Hu X, et al. Antibiotic de-escalation principle in elderly patients with chronic obstructive pulmonary disease complicated with severe pneumonia[J]. Experimental & Therapeutic Medicine, 2017, 13(4): 1485-1489

[30] Liu S, Zhou Y, Liu S, et al. Association between exposure to ambient particulate matter and chronic obstructive pulmonary disease: results from a cross-sectional study in China[J]. Thorax, 2017, 72(9): 788-795