doi: 10.13241/j.cnki.pmb.2017.09.037

戈利木单抗联合雷公藤多甙对甲氨蝶呤治疗反应不佳活动性类风湿关节炎的效果及安全性分析 *

刘婧依 陈赵玲 刘歧焕△ 鱼 强 薛 颖 徐延洁

（十堰市东风汽车公司总医院血液风湿内科 湖北 十堰 442008）

摘要 目的：分析戈利木单抗联合雷公藤多苷对甲氨蝶呤(MTX)治疗反应不佳活动性类风湿关节炎(RA)的临床效果及安全性。**方法：**选择 MTX 治疗反应不佳(MTX 治疗超 3 个月，但应答不足)的活动性 RA 患者 66 例，按照随机数字表法分为对照组与试验组各 33 例，对照组单用雷公藤多苷治疗，试验组加用戈利木单抗治疗，测定两组治疗前后血沉(ESR)、C 反应蛋白(CRP)、类风湿因子(RF)水平的变化，记录晨僵时间、关节肿胀数目、关节压痛数目，评定治疗效果，采用视觉模拟评分法(VAS)评定患者关节疼痛程度、患者对疾病总体症状的耐受情况，监测两组不良事件的发生情况。**结果：**① 治疗后，两组 ESR、CRP、RF 均降低，与同组治疗前对比差异有统计学意义(P<0.05)，试验组 ESR、CRP 降低幅度高于对照组(P<0.05)；② 治疗后，两组晨僵时间减少、关节肿胀及压痛数目均减少，与治疗前对比差异有统计学意义(P<0.05)，试验组各指标改善幅度均高于对照组(P<0.05)；③ 治疗后，两组 VAS 评分均降低，与治疗前对比差异有统计学意义(P<0.05)，试验组降低幅度高于对照组(P<0.05)；④ 试验组 ACR50、ACR70 所占比例均高于对照组(P<0.05)；⑤ 试验组、对照组不良反应发生率对比差异无统计学意义(P>0.05)。**结论：**戈利木单抗联合雷公藤多苷治疗 MTX 反应不佳活动性 RA 疗效肯定，可下调患者 ESR、CRP 水平，缩短晨僵时间，显著改善患者症状，减轻关节疼痛程度，且安全性高。

关键词：类风湿关节炎；雷公藤多苷；戈利木单抗；甲氨蝶呤；安全性

中图分类号：R593.22 **文献标识码：**A **文章编号：**1673-6273(2017)07-1735-04

Analysis of the Clinical Effects and Safety of Golimumab combined with Tripterygium Glycosides on the Rheumatoid Arthritis patients with Poor Response to Methotrexate*

LIU Jing-yi, CHEN Zhao-ling, LIU Qi-huan△, YU Qiang, XUE Ying, XU Yan-jie

(Department of Hematology and rheumatology, General Hospital of Dongfeng Motor Corporation, Shiyan, Shiyan, Hubei, 442008, China)

ABSTRACT Objective: To analyze the clinical effects and safety of golimumab combined with tripterygium glycosides on the rheumatoid arthritis (RA) patients with poor response to methotrexate (MTX). **Methods:** 66 RA patients with poor response to MTX (MTX treatment > 3 months, but lack of response) were selected and randomly divided into the control group and the test group (33 cases in each group), the control group received simple tripterygium glycosides, the test group added golimumab, erythrocyte sedimentation rate (ESR), C reactive protein (CRP) and changes of rheumatoid factor level in the two groups before and after the treatment were measured, the morning rigidity time, the number of swollen joints and the number of painful joints were recorded, treatment effect were evaluated, visual analogue scale (VAS) was used to assess degree of joint pain of patients and tolerance of patients to general symptoms of disease, occurrence of adverse events in the two groups were monitored during the test. **Results:** ① after the treatment, ESR, CRP and RF in the two groups were significantly reduced compared with the same group before the treatment (P<0.05), decrease of ESR and CRP in the test group were significantly higher than the control group (P<0.05); ② after the treatment, the morning rigidity time, the number of swollen joints and the number of painful joints were significantly reduced compare with those before the treatment (P<0.05), improvement range of all indexes in the test group were significantly higher than the control group (P<0.05); ③ after the treatment, VAS scores of the two groups were significantly decreased, there was a significant difference compared with those before the treatment (P<0.05), decrease of the test group was significantly higher than the control group (P<0.05); ④ proportion of ACR50 and ACR70 in the test group were significantly higher than the control group (P<0.05); ⑤ there was no significant difference in adverse reaction rate between the test group and the control group (P>0.05). **Conclusions:** Golimumab combined with tripterygium glycosides had good efficiency and safety on the RA patients with poor response to MTX, which could down-regulate the patients' ESR and CRP levels, shorten the morning rigidity time, improve patients' symptoms greatly, reduce degree of joint pain.

Key words: Rheumatoid arthritis; Tripterygium glycosides; Golimumab; Methotrexate; Safety

---

* 基金项目：湖北省科技攻关项目(2008ZD033)

作者简介：刘婧依(1982-)，硕士，主治医师，研究方向：血液病、风湿免疫疾病，电话：15607288167，E-mail：lssclf@163.com

△ 通讯作者：刘歧焕，liuqihuan-392@163.com

(收稿日期：2016-09-26 接受日期：2016-10-25)

Chinese Library Classification(CLC): R593.22 Document code: A
Article ID: 1673-6273(2017)07-1735-04

前言

类风湿关节炎(rheumatoid arthritis,RA)为临床常见抗原介导自身免疫性疾病,病理改变以滑膜增生、炎症细胞浸润、软骨组织破坏为主,造成关节畸形,以老年女性群体多见,近年来发病率有所上升[1]。临床上对 RA 治疗多采用物理干预、外科手术及药物治疗等方式,其中药物干预以糖皮质激素类、非甾体抗炎药(NSAIDs)、抗风湿药(DMARDs)等为主[2]。甲氨蝶呤为非生物型 DMARDs,早期多将其作为 RA 首选治疗药物。但近年来研究[3]显示长程、频繁应用 MTX 可能导致胃肠功能紊乱,诱发血液系统、肝脏系统等不良反应,且 MTX 单药对部分活动性 RA 患者疗效有限,目前多建议当 MTX 单药无法控制疾病进展时,添加肿瘤坏死因子(TNF-α)抑制剂或予以转换治疗以改善疗效[4]。戈利木单抗为新型 TNF-α 抑制剂,为 TNF-α 特异性人 IgG 单克隆抗体,可作用于滑膜细胞、破骨细胞,控制 RA 进展,减轻局部炎症,下调 CPR、血管内皮因子(VEGF)。且戈利木单抗与其他抗风湿类药物联用是当前活动性 RA 治疗研究的热点。基于此,为探讨戈利木单抗联合雷公藤多苷治疗对 MTX 反应不佳活动性 RA 患者的疗效及安全性,我院对收治的 66 例患者展开了研究,现报道如下:

1 资料与方法

1.1 一般资料

选择 2011 年 1 月 -2015 年 4 月我院收治的 66 例 MTX 治疗反应不佳的活动性 RA 患者。其中男 12 例,女 54 例;年龄 35-79 岁,平均(58.9± 4.9)岁;病程 2-9 年,平均(5.7± 1.4)年;体重 (60.8± 5.7)kg。按随机数字表法分为对照组与试验组各 33 例。对照组中男 5 例,女 28 例;年龄 36-78 岁,平均(59.3± 4.5)岁;病程(5.8± 1.5)年;体重(60.7± 5.8)kg。试验组男 7 例,女 26 例;年龄 35-78 岁,平均(59.9± 4.8)岁;病程(5.6± 1.7)年;体重(60.5± 5.9)kg。两组性别、年龄、体重、病程等资料对比差异无统计学意义(P>0.05),且本试验经我院伦理委员会审批通过。

1.2 方法

对照组采用雷公藤多苷 (江苏美通制药有限公司生产,规格:10 mg× 50 s,批号:Z32021007)治疗,20 mg/ 次,3 次 /d。试验组在次基础上加用戈利木单抗(Centocor Ortho Biotech Inc 生产,规格:50 mg/0.5 mL/ 支),皮下注射,50 mg/ 次,2 次 / 周。两组总疗程均为 3 个月。

1.3 诊断标准

纳入标准:① 符合美国风湿病学会(ACR)通过的 RA 诊断标准[5],疾病处于活动期,关节肿胀数目≥ 4 个,关节压痛数目≥ 6 个,ESR 或 CPR 异常或晨僵持续时间≥ 45 min; ② 曾接受 MTX 治疗≥ 3 个月,但病情改善不明显;③ 知情研究内容,自愿签署研究同意书。排除标准:① 合并肝炎、肺炎、肾炎或伴严重感染者;② 既往有活动性肺结核史;③ 乙肝、丙肝或艾滋病者;④ 合并恶性肿瘤、多发性硬化或严重心、肝、肾、肺、血液系统疾病者;⑤ 内分泌疾病者;⑥ 妊娠或哺乳期女性;⑦ 入组前 1 个月接受其他影响试验结果的 DMARDs 治疗或既往接受 TNF 抑制剂治疗者;⑧ 依从性差,不能完成治疗或中途退出者。

1.4 观察指标

两组均于治疗前、治疗 3 个月后观察各项。① 取治疗前后空腹肘静脉血 3 mL,测定 ESR、CRP、RF 的变化。② 观察两组治疗前后晨僵时间、关节肿胀数目、关节压痛数目的变化。③ 采用 VAS 表[6]评定患者关节疼痛程度、患者对疾病的耐受程度、医生对患者疾病耐受程度的评定,总分 0-10 分,0 分为正常,10 分为无法耐受,评分越高,表示疼痛程度越高、耐受度越差。④ 参照 ACR 制定的活动性 RA 疗效评定标准[7]评估治疗效果,统计达到 ACR20、ACR50、ACR70 所占比例。ACR20:压痛关节数改善超过 20%;肿胀关节数目改善超过 20%;患者疼痛评估、疾病活动性总体评估、医生对疾病活动性评价、血沉、CRP 或 RF 急性时相反应物 5 项中,3 项改善超过 20%;ACR50 指各项改善率超过 50%;ACR70 指各项指标改善超过 70%。⑤ 监测试验期间均监测患者肝肾功能、血尿常规,记录治疗过程中不良事件发生率。

1.5 统计学分析

用 SPSS19.0 软件处理数据,计数资料行 x^2 检验,计量资料采用 t 检验,以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组治疗前后 ESR、CRP、RF 水平比较

治疗前,两组 ESR、CRP、RF 对比差异无统计学意义(P>0.05)。治疗后,两组各指标均降低,与治疗前对比差异有统计学意义 (P<0.05),试验组 ESR、CRP 降低幅度高于对照组(P<0.05),如表 1。

表 1 两组治疗前后 ESR、CRP、RF 水平比较($\bar{x}$± s)

Table 1 Comparison of the ESR, CRP and RF levels before and after the treatment between the two groups ($\bar{x}$± s)

Groups	ESR(mm/h)		CRP(mg/L)		RF(IU/mL)	
	Before the treatment	After the treatment	Before the treatment	After the treatment	Before the treatment	After the treatment
Test group	58.35± 22.44	25.05± 15.23*△	35.35± 20.14	14.21± 10.23*△	884.23± 986.15	182.21± 276.22*
Control group	58.36± 22.48	38.16± 17.23*	35.38± 20.13	20.99± 6.25*	885.25± 980.18	208.64± 198.74*

Note: Compared with the same group before the treatment: *P<0.05, compared with the control group after the treatment: △ P<0.05.

2.2 两组治疗前后各临床指标比较

治疗前,两组各临床指标对比差异无统计学意义(P>0.05)。治疗后,两组晨僵时间减少、关节肿胀及压痛数目均减少,与治疗前对比差异有统计学意义(P<0.05),但试验组各指标改善幅

度均高于对照组(P<0.05),如表 2。

表 2 两组治疗前后各临床指标比较($\bar{x}\pm$ s)

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

Groups	The morning rigidity time(min)		The number of swollen joints (case)		The number of painful joints (case)	
	Before the treatment	After the treatment	Before the treatment	After the treatment	Before the treatment	After the treatment
Test group	65.26± 5.27	22.26± 4.19*△	12.21± 6.54	3.73± 0.94*△	13.24± 5.47	3.11± 1.41*△
Control group	65.28± 5.26	31.65± 5.47*	12.22± 6.57	5.21± 0.78*	13.25± 5.49	5.84± 2.14*

Note: Compared with the same group before the treatment: *P<0.05, compared with the control group after the treatment: △ P<0.05.

2.3 两组治疗前后关节疼痛 VAS、患者自我评价 VAS 及医生评价 VAS 比较

治疗前，两组关节疼痛 VAS、自我评价及医生评价 VAS 对比差异无统计学意义(P>0.05)。治疗后,两组评分均降低,与治疗前对比差异有统计学意义(P<0.05),试验组降低幅度高于对照组(P<0.05),如表 3。

表 3 两组治疗前后关节疼痛 VAS、患者自我评价 VAS 及医生评价 VAS 比较($\bar{x}\pm$ s,分)

Table 3 Comparison of joint pain VAS, patient self evaluation VAS and doctor evaluation VAS before and after the treatment betwen the two groups ($\bar{x}\pm$ s, scores)

Groups	Painful joints		Self assessment		Doctor evaluation	
	Before the treatment	After the treatment	Before the treatment	After the treatment	Before the treatment	After the treatment
Test group	8.45± 2.44	3.36± 1.48*△	8.46± 2.14	3.38± 1.25*△	8.38± 1.99	3.41± 1.30*△
Control group	8.46± 2.39	5.21± 1.59*	8.49± 2.17	5.25± 1.48*	8.39± 2.03	5.18± 1.26*

Note: Compared with the same group before the treatment: *P<0.05, compared with the control group after the treatment: △ P<0.05.

2.4 两组治疗效果比较

试验组 ACR50、ACR70 所占比例均高于对照组,差异有统计学意义(P<0.05),如表 4。

表 4 两组治疗效果比较[例(%)]

Table 4 Comparison of treatment effects between the two groups [n (%)]

Groups	n	ACR20	ACR50	ACR70
Test group	33	26(78.79)	22(66.67)*	12(36.36)*
Control group	33	23(69.70)	12(36.36)	4(12.12)

Note: Compared with the control group: *P<0.05.

2.5 两组治疗不良反应发生率比较

两组各治疗不良反应发生率对比差异无统计学意义(P>0.05),如表 5。

表 5 两组治疗不良反应发生率比较[例(%)]

Table 5 Comparison of the occurrence rates of adverse reactions between the two groups [n (%)]

Groups	n	Infection	Local swelling and pain	Abnormal liver function	Gastrointestinal reaction
Test group	33	4(12.12)	2(6.06)	1(3.03)	4(12.12)
Control group	33	2(6.06)	3(9.09)	2(6.06)	3(9.09)

3 讨论

RA 是一组以外周关节炎性反应为特点的多器官自身免疫性疾病,患者伴长期病痛感,活动能力降低,严重者可能出现关节畸形,导致残疾[8]。RA 治疗的目标旨在防止骨髓受损,阻止肌腱、韧带破裂与软骨降解所引起的功能性损害[9]。研究[10]显示骨炎、滑膜炎等持续性炎症及机体持续性炎症是预示后续结构性损伤的关键表现,炎症也是造成疲劳、疼痛、残疾的重要原因。

甲氨蝶呤是治疗 RA 的基本药物，对 RA 患者疗效肯定，但长期服用甲氨蝶呤患者可能出现脱发、血小板计数降低、肝功能异常及严重胃肠道反应等不良事件,且服药剂量越大,不良反应发生率越高,导致患者服药依从性降低,药效反应不佳[11]。文献研究[12]显示对甲氨蝶呤单药不能有效控制 RA 时,一般建议添加 TNF 抑制剂或其他生物制剂联用,减轻机体炎性反应,达到治疗的目的。雷公藤多苷主要成分为雷公藤提取物,包含半萜类、二萜类、三萜类化合物,其中雷公藤甲素为具代表性环氧二萜类成分,药理实验[13]表明其有明显的抗炎、抗肿瘤及免疫抑制作用。其主要机制与雷公藤抑制促炎基因表达,下调白介素 2、TNF-α、环氧化酶 -2 及诱导型一氧化氮氧合酶有关,且雷公藤甲素可作用于 T 淋巴系统、糖皮质激素受体 -1 复合物,

抑制 TNF-α 转录,阻断炎症反应细胞核因子 -kB 活化。且吴少辉[14]等发现与传统 DMRADs 药物相比,雷公藤多苷可诱导滑膜成纤细胞凋亡,药效更为明显,可消肿止痛、祛风除湿、清热解毒。但同时还需注意,雷公藤多苷用药同时存在诸多不良反应,包括肝肾、血液、神经系统损害及女性生殖系统损害等。

近期也有研究者[15,16]表示 TNF-α 抑制剂与雷公藤多苷联合用于 RA 治疗效果优于 DMARDs 单药治疗。戈利木单抗为新型人抗 TNF 单克隆抗体,能与跨膜活性及可溶性形式的 TNF-α 结合,阻断其与 TNF 受体结合,抑制其生物活性[17]。TNF 是导致 RA 患者出现关节炎症的关键介质,而戈利木单抗可调节 TNF 介导生物学效应,下调白细胞浸润粘附蛋白表达,抑制炎性细胞因子分泌,其在体外与可溶性人 TNF-α 结合效应与依那西普类似,且高于阿达木单抗与英夫利西单抗[18,19]。本研究中,对照组单用雷公藤多苷治疗,试验组在此基础上加用戈利木单抗联合治疗,结果显示治疗后试验组 ESR、CRP 降低幅度均高于对照组(P<0.05);同时患者晨僵时间缩短、关节肿胀及压痛数目减少,与对照组相比差异有统计学意义(P<0.05);VAS 评分结果显示试验组关节疼痛、自我评价、医生评价 VAS 评分结果均低于对照组,同时其 ACR50、ACR70 所占比例高于对照组(P<0.05),与兰芬[20]等报道结果类似。且安全性监测显示两组不良反应发生率对比差异无统计学意义 (P>0.05),证实加用 TNF 抑制剂戈利木单抗不会增加不良反应发生率。

综上所述,采用戈利木单抗联合雷公藤多苷治疗 MTX 反应不佳活动性 RA 疗效肯定,可显著下调患者 ESR、CRP 水平,改善关节压痛、肿胀症状,缩短晨僵时间,减轻关节疼痛程度,且安全性较高。

参 考 文 献(References)

[1] 吕倩雯, 张烜. 比较雷公藤多甙和甲氨蝶呤对治疗活动性类风湿关节炎的有效性与安全性[J]. 中华内科杂志, 2015, 54(6): 537
Lv Qian-wen, Zhang Xuan. Comparison of effectiveness and safety of tripterygium glycosides and methotrexate in the treatment of rheumatoid arthritis[J]. Chinese Journal of Internal Medicine, 2015, 54(6): 537

[2] 余静, 谢其冰, 鲍晓, 等. 白芍总苷胶囊联合正清风痛宁片治疗类风湿关节炎疗效观察[J]. 西部医学, 2015, 27(7): 992-995
Yu Jing, Xie Qi-bing, Bao Xiao, et al. Total glucosides of paeony capsule combined with Zhengqing Fengtongning tablet in treatment of rheumatoid arthritis [J]. Medical Journal of West China, 2015, 27(7): 992-995

[3] 杨奕, 刘重阳, 刁建萍, 等. 甲氨蝶呤联合免疫吸附治疗类风湿关节炎疗效分析[J]. 实用医学杂志, 2013, 29(14): 2376-2378
Yang Yi, Liu Chong-yang, Diao Jian-ping, et al. Analysis of efficacy of methotrexate combined with immunoadsorption therapy in the treatment of rheumatoid arthritis [J]. The Journal of Practical Medicine, 2013, 29(14): 2376-2378

[4] 张榕, 吴春玲, 李舒帆, 等. 雷公藤多甙联合来氟米特治疗老年活动性类风湿关节炎的疗效 [J]. 中国老年学杂志, 2011, 31(12): 2194-2196
Zhang Rong, Wu Chun-ling, Li Shu-fan, et al. Efficacy of tripterygium glycosides combined with leflunomide in the treatment of active rheumatoid arthritis in the elderly[J]. Chinese Journal of Gerontology, 2011, 31(12): 2194-2196

[5] 徐丽玲, 苏茵. 2015 年美国风湿病学会类风湿关节炎的治疗指南[J]. 中华风湿病学杂志, 2016, 20(1): 69-70
Xu Li-ling, Su Yin. Guidelines for the treatment of rheumatoid arthritis in American college of rheumatology in 2015 [J]. Chinese Journal of Rheumatology, 2016, 20(1): 69-70

[6] 曹卉娟, 邢建民, 刘建平, 等. 视觉模拟评分法在症状类结局评价测量中的应用[J]. 中医杂志, 2009, 50(7): 600-602
Cao Hui-juan, Xing Jian-min, Liu Jian-ping, et al. Application of Visual Analogue Scales in Assessment of Symptomatic Outcome Data [J]. Journal of Traditional Chinese Medicine, 2009, 50(7): 600-602

[7] 赵金霞, 苏茵, 刘湘源, 等. 早期类风湿关节炎分类标准及其诊断意义的探讨[J]. 中华风湿病学杂志, 2012, 16(10): 651-656
Zhao Jin-xia, Su Yin, Liu Xiang-yuan, et al. Establishment and evaluation of classification criteria for early rheumatoid arthritis [J]. Chinese Journal of Rheumatology, 2012, 16(10): 651-656

[8] 郭静波, 李亮, 马振勇, 等. 依那西普联合雷公藤饮片治疗类风湿关节炎的临床观察[J].解放军医药杂志, 2011, 23(4): 31-33
Guo Jing-bo, Li Liang, Ma Zhen-yong, et al. Clinical Observation of Etananercept Combined with Tripterygium in Treatment of Rheumatoid Arthritis [J]. Medical Journal of Chinese people's Liberation Army, 2011, 23(4): 31-33

[9] 马亚, 曾学军.甲氨蝶呤治疗类风湿关节炎的新思考[J]. 基础医学与临床, 2012, 32(3): 354-357
Ma Ya, Zeng Xue-jun. Methotrexate is a new consideration in treatment of rheumatoid arthritis [J]. Basic & Clinical Medicine, 2012, 32(3): 354-357

[10] 刘敏, 王培蓉, 马方伟, 等. 雷公藤多苷治疗类风湿性关节炎的临床观察及对血清 VEGF,VEGFR2 表达水平的影响研究[J]. 陕西中医, 2016, 37(1): 72-74
Liu Min, Wang Pei-rong, Ma Fang-wei, et al. The clinical curative effects of tripterygium glycosides and the expression levels of serum VEGF, VEGFR2 for the patients with rheumatoid arthritis[J]. Shaanxi Journal of Traditional Chinese Medicine, 2016, 37(1): 72-74

[11] Oliveira R D R, Fontana V, Junta C M, et al. Differential gene expression profiles may differentiate responder and nonresponder patients with rheumatoid arthritis for methotrexate (MTX) monotherapy and MTX plus tumor necrosis factor inhibitor combined therapy [J]. The Journal of rheumatology, 2012, 39(8): 1524-1532

[12] 张霞, 叶华. 戈利木单抗联合甲氨蝶呤治疗中国成人活动性类风湿关节炎的有效性与安全性 [J]. 中华内科杂志, 2016, 55(3): 229-230
Zhang Xia, Ye Hua. Effectiveness and safety of golimumab combined with methotrexate in the treatment of active rheumatoid arthritis in Chinese adults [J]. China Journal of Internal Medicine, 2016, 55(3): 229-230

[13] 李文思, 陈璋璋, 吕迁洲, 等. 肿瘤坏死因子α-308G/A 多态性与类风湿关节炎疾病及肿瘤坏死因子 α 抑制剂疗效的相关性研究进展[J]. 临床内科杂志, 2015, 32(8): 570-572
Li Wen-si, Chen Zhang-zhang, Lyv Qian-zhou, et al. Research progress of tumor necrosis factor α-308G/A polymorphism and rheumatoid arthritis and tumor necrosis factor α inhibitor efficacy[J]. Journal of Clinical Internal Medicine, 2015, 32(8): 570-572

(下转第 1725 页)

Wang Xin, Ma Chun-yan, Zhang Ya-jing, et al. Expression of peripheral Th1/Th2 and clinical significance of the change of pul monary function in; children with mycoplasma pneumoniae pneumonia [J]. Chinese Journal of Clinicians (Electronic Edition), 2014, 14 (6): 1031-1035

[11] 刘爽, 赵素红, 王丹丹, 等. 布地奈德混悬液吸入对支原体肺炎患儿肺功能及炎性状态的影响 [J]. 中国妇幼保健, 2012, 27(15): 2360-2362
Liu Shuang, Zhao Su-hong, Wang Dan-dan, et al. Effect of inhalation of budesonide suspension on pulmonary function and inflammatory status of children with mycoplasma pneumonia [J]. Maternal & Child Health Care of China, 2012, 27(15): 2360-2362

[12] 康钰, 郭利明. 布地奈德混悬液联合阿奇霉素序贯治疗幼儿支原体肺炎[J]. 西部医学, 2015, 27(12): 1842-1844, 1850
Kang Yu, Guo Li-ming. Budesonide suspension and sequential azithromycin for treatment of children with Mycoplasma pneumonia [J]. Medical Journal of West China, 2015, 27(12): 1842-1844, 1850

[13] 李立学, 汪桂香, 刘燕, 等. 抗生素联合糖皮质激素治疗儿童重症支原体肺炎的临床效果分析 [J]. 中国医学前沿杂志（电子版), 2016, 8(2): 50-52
Li Li-xue, Wang Gui-xiang, Liu Yan, et al. Clinical effect of antibiotic combined with glucocorticoid in the treatment of children with severe myco- plasma pneumonia[J]. Chinese Journal of the Frontiers of Medical Science (Electronic Version), 2016, 8(2): 50-52

[14] 张祥. 糖皮质激素治疗难治性肺炎支原体肺炎的临床观察 [J]. 临床肺科杂志, 2015, 15(8): 1472-1475
Zhang Xiang. Clinical study of glucocorticoid in the treatment of refractory mycoplasma pneumoniae pneumonia [J]. Journal of Clinical Pulmonary Medicine, 2015, 15(8): 1472-1475

[15] 吴勇, 蔡俊伟, 李立浩, 等. 重症肺炎支原体肺炎患儿的肺功能变化及临床意义[J]. 吉林医学, 2015, 15(13): 2743-2744
Wu Yong, Cai Jun-wei, Li Li-hao, et al. Study on the changes of Pulmonary functions in children with insevere Mycoplasma pneumoniae pneumonia[J]. Jilin Medical Journal, 2015, 15(13): 2743-2744

[16] 周彩丽, 贾云乔, 刘宗伟, 等. 儿童难治性肺炎支原体肺炎肺功能的变化规律及临床意义 [J]. 中国妇幼保健, 2016, 31(19): 3952-3955
Zhou Cai-li, Jia Yun-qiao, Liu Zong-wei, et al. Change regularity and clinical significance of pulmonary function in children with refractory Mycoplasma pneumoniae pneumonia [J]. Maternal & Child Health Care of China, 2016, 31(19): 3952-3955

[17] 梁粤. 肺炎支原体肺炎患儿外周血 IL-10/IL-17 表达与肺功能变化的相关性研究[J]. 临床儿科杂志, 2015, 15(8): 686-689
Liang Yue. PeripheralIL-10/IL-17 expression and pulmonary function in children withMycoplasma pneumoniae pneumonia [J]. Journal of Clinical Pediatrics, 2015, 15(8): 686-689

[18] 蔡金龙, 李航, 曲书强, 等. 肺炎支原体肺炎患儿的肺功能特点及临床意义[J]. 中国医师进修杂志, 2016, 39(5): 437-439
Cai Jin-long, Li Hang, Qu Shu-qiang, et al. The characteristics and clinical significance of lung function in children with mycoplasma pneumoniae pneumonia [J]. Chinese Journal of Postgraduates of Medicine, 2016, 39(5): 437-439

[19] 邓香. 儿童肺炎支原体肺炎影像学及肺功能特点 [J]. 中外医学研究, 2014, 14(34): 58-59, 60
Deng Xiang. The Imaging Feature and the Lung Function Changes of Mycoplasma Pneumoniae Pneumonia in Children [J]. Chinese and Foreign Medical Research, 2014, 14(34): 58-59, 60

[20] 赵艳飞. 糖皮质激素对重症肺炎支原体肺炎患儿免疫功能的影响[J]. 医学综述, 2014, 20(21): 4011-4012
Zhao Yan-fei. Study on the Effect of Glucocorticoid on the Immune Function of Children with Refractory Mycoplasma Pneumoniae Pneumonia[J]. Medical Recapitulate, 2014, 20(21): 4011-4012

（上接第 1738 页）

[14] 吴少辉, 刘光明. 雷公藤内酯的提取、分析和药理作用研究进展[J]. 现代药物与临床, 2011, 26(1): 36-39
Wu Shao-hui, Liu Guang-ming. Advances in study on triptolide extraction, analysis, and its pharmacological effects [J]. Drugs & Clinic, 2011, 26(1): 36-39

[15] 刘玉英, 范红松, 徐峰, 等. 抗环瓜氨酸肽抗体联合类风湿因子在检测类风湿关节炎中的临床价值[J]. 现代生物医学进展, 2013, 13(31): 6102-6105
Liu Yu-ying, Fan Hong-song, Xu Feng, et al. Clinical Value of Anti-cyclic Citrulinated Peptid Antibody(Anti-CCP) Joint Rheumatoidfactor(RF)in the Detection of Rheumatoid Arthritis(RA)[J]. Progress in Modern Biomedicine, 2013, 13(31): 6102-6105

[16] VanDerHeijden J W, Assaraf Y G, Gerards A H, et al. Methotrexate analogues display enhanced inhibition of TNF-α production in whole blood from RA patients [J]. Scandinavian journal of rheumatol- ogy, 2014, 43(1): 9-16

[17] Yanshan Li, Lindi Jiang, Si Zhang, et al. Methotrexate attenuates the Th17/IL-17 levels in peripheral blood mononuclear cells from healthy individuals and RA patients[J]. Rheumatology international, 2012, 32 (8): 2415-2422

[18] Elisabeth Lie, Till Uhlig, Desireevd H, et al. Effectiveness of sulfasalazine and methotrexate in 1102 DMARD-naive patients with early RA[J]. Rheumatology, 2012, 51(4): 670-678

[19] Lee S W, Kim J H, Park M C, et al. Alleviation of rheumatoid arthritis by cell-transducible methotrexate upon transcutaneous delivery[J]. Biomaterials, 2012, 33(5): 1563-1572

[20] 兰芬, 阳凌燕, 管剑龙, 等. 类风湿关节炎治疗药物的研究进展[J]. 药学服务与研究, 2013, 13(1): 38-42
Lan Fen, Yang Ling-yan, Guan Jian-long, et al. Advances in research on drugs for the treatment of rheumatoid arthritis [J]. Pharmaceutical Care and Research, 2013, 13(1): 38-42