doi: 10.13241/j.cnki.pmb.2017.15.026

老年类风湿关节炎患者应用 MTX 或 LEF 联合糖皮质激素治疗的效果观察 *

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摘要 目的：探讨甲氨蝶呤（MTX）或来氟米特（LEF）联合泼尼松（PDN）对老年类风湿关节炎的疗效。**方法：**选取 112 例老年 RA 患者，按随机数表法将患者分为 LEF 组（n=28）、MTX 组（n=28）、LET+PDN 组（n=28）、MTX+PDN 组（n=28），治疗 3 个月后统计四组关节肿胀数、关节压痛数、DAS28 评分、VAS 评分、RF、晨僵时间，并记录不良反应事件。**结果：**MTX 组和 LEF 组治疗后各项指标均低于治疗前（P<0.05）；MTX+PDN 组与 LEF+PDN 组治疗后各项指标均明显低于治疗前（P<0.001）；MTX+PDN 组治疗效果明显优于 MTX 组（P<0.001）；LEF+PDN 组治疗效果明显优于 LEF 组（P<0.001）；MTX+PDN 组治疗总有效率为 53.57%，高于 LEF+PDN 组的 42.86%，但差异无统计学意义（x^2=2.426，P=0.119）。**结论：**四组对 RA 均有治疗效果，联合使用效果更佳，且服药后无严重不良反应，安全性较高。

关键词：类风湿关节炎；泼尼松；甲氨蝶呤；来氟米特

中图分类号：R593.22 **文献标识码：**A **文章编号：**1673-6273（2017）15-2903-04

Observation on the Effect of MTX or LEF Combined with Glucocorticoid in the Treatment of Elderly Patients with Rheumatoid Arthritis*

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ABSTRACT Objective: To investigate the curative effect of methotrexate (MTX) or leflunomide (LEF) in combination with prednisone (PDN) in the treatment of senile rheumatoid arthritis (RA). **Methods:** 112 elderly patients with RA in our hospital between May 2013 and November 2015 were selected. All patients were divided into LEF group (n=28), MTX group (n=28), LET+PDN group (n=28), MTX+PDN group (n=28) according to the random number table method. After 3 months of treatment, calculate the swollen joints, joint tenderness, DAS28 score, VAS score, RF, morning stiffness time and record the adverse events. **Results:** The indexes of MTX group and LEF group after treatment were significantly lower than before treatment (P<0.05). The indexes of MTX+PDN group and LEF+PDN group were also significantly lower after treatment than before treatment, and the difference was statistically significant (P<0.001). MTX+PDN group showed significantly better effect than MTX group (P<0.001), and LEF+PDN group also showed significantly better effect than LEF group (P<0.001). The total effective rate of MTX+PDN group was 53.57%, higher than that of 42.86% in LEF+PDN group, but the difference was not statistically significant (x^2=2.426, P=0.119). **Conclusion:** The four groups all had curative effect, but the combination of two had better effect, and there were no serious adverse reactions after treatment. The efficacy difference between MTX+PDN group and LEF+PDN group was not distinct, so they can be selected according to the actual situation.

Key words: Rheumatoid arthritis; Prednisone; Methotrexate; Leflunomide

Chinese Library Classification(CLC): R593.22 Document code: A

Article ID: 1673-6273(2017)15-2903-04

前言

风湿性关节炎（rheumatic arthritis，RA）是一种常见的急性/慢性结缔组织炎症，可反复发作并累及心脏。临床症状主要包括关节和肌肉游走性酸楚、重著、疼痛，是风湿热的主要表现之一，起病原因常有急性发热及关节疼痛[1]。其发病机制目前尚未清楚，目前治疗方法较多，但均不能有效治愈[2]。常见的治疗药物包括糖皮质激素、非甾体抗炎药及各种抗风湿药，而老年风

* 基金项目：新疆维吾尔自治区自然科学基金项目（2014211C078）
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（收稿日期：2016-08-19 接受日期：2016-09-20）

湿病因常常多种,临床选择联合多种药物一起治疗,希望获得更好的疗效。本研究分析比较氟米特(leflunomide,LEF)、甲氨蝶呤(methotrexate,MTX)和泼尼松(prednison,PDN)三种药物单独和联合使用的疗效差异。

1 资料与方法

1.1 一般资料

选取我院 2013 年 5 月至 2015 年 11 月期间收治的老年 RA 患者 112 例,其中男性 25 例,女性 87 例,年龄为 58～77 岁,平均年龄为(63.87± 3.92)岁,病程为 6 个月～4 年,平均病程为(1.74± 0.62)年。根据随机数表法将所有患者分为 LEF 组(n=28)、MTX 组(n=28)、LET+PDN 组(n=28)、MTX+PDN 组(n=28)。四组患者年龄分部、性别比例及病程等差异无统计学意义(P<0.05)。本研究为前瞻性实验,经院伦理协会批准,并或者患自愿签署知情同意书。

1.2 纳入与排除标准

纳入标准[3]:1)有 3 个或 3 个以上的关节部位的软组织肿胀(关节炎);2)早晨起来关节僵硬,持续至少 1 小时;3)掌指关节、近端指间关节或腕关节肿胀超过 6 周;4)皮下类风湿结节;5)对称性肿胀(关节炎);6)X 线片显示手和(或)腕关节软骨面呈糜烂样和(或)关节周围骨质稀疏改变;7)类风湿因子阳性。诊断条件满足以上 3 点即可。排除标准[4,5]:1)合并严重心肝肾疾病或其他内分泌系统疾病;2)伴有严重肠胃功能不全或消化疾病;3)3 个月内曾接受糖皮质激素或抗风湿药物的治疗;4)对 LEF、MTX 或 PDN 敏感;5)身体严重虚弱或怀孕患者。

1.3 方法[6]

LEF 组:给予 LEF 20 mg,1 次 / 天,口服;MTX 组:给予 MTX 15 mg,1 次 / 天,口服;MTX 联合 PDN 组:MTX 15 mg+PDN 10 mg,1 次 / 天, 口服;LEF 联合 PDN 组:LEF 20 mg+PDN 10 mg,1 次 / 天,口服,四组均连续服用 3 个月。

1.4 观察及评价指标

统计四组治疗前后关节肿胀数、关节压痛数、DAS28 评分、视觉模拟评分法(VAS)评分、类风湿因子(Rheumatoid factor,RF)、晨僵时间[7]。并记录四组是否有恶心腹泻、发热和皮疹等药物不良反应症状。设置各项评价指标均改善程度在 40%以下为中, 各项指标均有改善, 评分及时间改善程度在 30%～70%为良, 各项指标均有显著改善, 评分及时间改善程度在 70%以上为优。

1.5 统计学方法

将本组关节肿胀数、关节压痛数、DAS28 评分、VAS 评分、RF、晨僵时间录入 SPSS 21.0 行数据分析,计数资料行 x^2 检验或确切概率法,计量资料用($\bar{x}\pm s$)表示,组间比较采用两样本 t 检验,如结果提示 P<0.05,差异存在统计学意义。

2 结果

2.1 对比 MTX 组与 MTX 联合 PDN 组各项指标

MTX 组治疗后关节压痛数、关节肿胀数、VAS 评分、DAS28 评分、晨僵时间和 RF 均明显低于治疗前(P<0.05);MTX+PDN 组治疗后关节压痛数、关节肿胀数、VAS 评分、DAS28 评分、晨僵时间和 RF 均明显低于治疗前(P<0.05);同期治疗后,与 MTX 组相比,MTX+PDN 组的关节压痛数(t=21.239,P<0.001),关节肿胀数(t=7.348,P<0.001),VAS 评分(t=12.379,P<0.001),DAS28 评分(t=5.714,P<0.001),晨僵时间(t=9.565,P<0.001)与 RF(t=12.637,P<0.001)等指标均明显要低,差异均有统计学意义(P<0.001)(表 1)。

表 1 MTX 组与 MTX 联合 PDN 组各项指标比较

Table 1 Comparison of the indexes between MTX group and MTX plus PDN group

Groups		Joint tenderness counts	Swollen joint counts	VAS scores	DAS28 scores	Morning stiffness time(min)	RF(IU/min)
MTX	Prior treatment	4.48± 0.32	2.76± 0.52	55.28± 3.90	5.11± 1.19	120.17± 5.86	495.33± 10.54
	Posttreatment	3.36± 0.20[a]	1.33± 0.34[a]	28.20± 4.40[a]	3.31± 0.74[a]	57.70± 4.87[a]	210.70± 11.81[a]
MTX+PDN	Prior treatment	4.86± 0.28	2.85± 0.41	56.32± 4.00	6.08± 0.98	125.74± 3.98	501.31± 12.36
	Posttreatment	2.28± 0.18[a,b]	0.76± 0.23[a,b]	17.53± 1.20[a,b]	2.21± 0.70[a,b]	46.72± 3.63[a,b]	170.71± 11.87[a,b]

Note: [a] compared with prior treatment, P<0.05; [b] compared with the MTX group at the same period, P<0.001.

2.2 LEF 组与 LEF 联合 PDN 组患者各项指标比较

LEF 组治疗后关节压痛数、关节肿胀数、VAS 评分、DAS28 评分、晨僵时间和 RF 均明显低于治疗前(P<0.05);LEF+PDN 组治疗后关节压痛数、关节肿胀数、VAS 评分、DAS28 评分、晨僵时间和 RF 明显低于治疗前义(P<0.05)。同期治疗后,与 LEF 组相比,LEF+PDN 组的关节压痛数·(t=4.2629,P=0.001),关节肿胀数 (t=6.721,P<0.001),VAS 评分(t=11.261,P<0.001),DAS28 评分(t=5.213,P<0.001),晨僵时间(t=8.912,P<0.001)与 RF(t=12.091,P<0.001)等指标均明显要低,差异均有统计学意义(P<0.001)(表 2)。

2.3 MTX+PDN 组与 LEF+PDN 组疗效分析

MTX+PDN 组疗效为中和良的比例与 LEF+PDN 组差异无统计学意义(P>0.05);MTX+PDN 组疗效为优的比例显著高于 LEF+PDN 组, 差异有统计学意义(x^2=8.139,P=0.004);MTX+PDN 组总有效率为 53.57%, 高于 LEF+PDN 组的 42.86%,差异无统计学意义(x^2=2.426,P=0.119(表 3)。

2.4 四组患者不良反应对比

服药期间 MTX 产生 2 例恶心呕吐,LEF 产生 1 例恶心呕吐,经过治疗后均无不适,对实验结果无影响。

表 2 LEF 组与 LEF 联合 PDN 组患者各项指标对比

Table 2 Comparison of the indexes between LEF group and LEF plus PDN group

Groups		Joint tenderness counts	Swollen joint counts	VAS score	DAS28 score	Morning stiffness time(min)	RF(IU/min)
LEF	prior treatment	4.51± 1.12	2.55± 0.49	56.32± 4.24	5.61± 0.87	121.30± 7.32	480.30± 10.38
	posttreatment	3.19± 0.91[a]	1.21± 0.30[a]	29.86± 3.56[a]	2.84± 0.73[a]	52.26± 6.28[a]	220.51± 9.40[a]
LEF+PDN	prior treatment	5.01± 1.24	3.02± 0.44	56.27± 5.30	5.56± 0.52	125.38± 8.29	498.48± 8.52
	posttreatment	2.24± 0.75[a b]	0.73± 1.15[a b]	18.48± 4.89[a b]	1.33± 0.44[a b]	43.21± 7.19[a b]	170.53± 7.20[a b]

Note: [a] compared with prior treatment, P<0.05; [b] compared with the LET group at the same period, P<0.001.

表 3 MTX+PDN 组与 LEF+PDN 组疗效比较

Table 3 Comparison of the curative effect between MTX + PDN group and LEF + PDN group

Groups	N	Medium	Good	Excellent	Total effective rate
MTX+PDN	28	13(46.43)	9(32.14)	6(21.43)	15(53.57)
LEF+PDN	28	16(57.14)	10(35.71)	2(7.15)	12(42.86)
x^2		2.422	0.202	8.139	2.426
P		0.119	0.653	0.004	0.119

3 讨论

RA 为慢性炎症病变的自身性免疫疾病，其表现部位包括全身关节，发病率随着年龄增长不断递增，老年发病率为较高，通常早 50 岁左右达到高峰值[8]。RA 发病过程缓慢，随着天气及机体自身因素而出现发作与缓解的交替现象，对患者的生活及身心健康均造成极大的影响，延治的患者可导致疾病缠绵难愈，严重者可出现关节变形甚至肢体残疾。临床研究对 RA 的发病机制未完全了解，国外研究表明 RA 的结局包括残疾、死亡、经济负担、药物毒发反应和痛苦[9]，药物能够缓解患者疼痛，控制和防止关节受损，现研究不同药物组合对 RA 的治疗效果。

根据实验结果可知 MTX、LEF 对 RA 均有治疗效果，治疗后关节压痛数、关节肿胀数、VAS 评分、DAS28 评分、晨僵时间和 RF 均低于治疗前，差异有统计学意义(P<0.05)。MTX 联合 PDN 组治疗效果与 LEF 联合 PDN 组的疗效均高于纯 MTX 组和纯 LEF 组，差异有统计学意义(P<0.05)。表明 PDN 能对提高 MTX 和 LEF 对 RA 的治疗效果，联合使用更加理想。MTX+PDN 组总有效率为 53.57%，高于 LEF+PDN 组的 42.86%，但差异无统计学意义(x^2=2.426，P=0.119)，证明两种药物治疗效果并未有显著差异，但从结果可知 MTX 联合 PDN 组的疗效较 LEF 联合 PDN 组更好一些。在不良反应中，MTX 产生 2 例恶心呕吐，LEF 产生 1 例恶心呕吐，差异并不明显，猜测与例数过少有关。在国内临床试验中，LEF 组不良反应发生率和严重不良反应均显著低于 MTX 组[10]。

MTX 和 LEF 均属于典型的治疗风湿类药物，其本身并不具备抗炎作用，但对疾病的缓解有一定作用。其中 MTX 为抗风湿药物首选，非甾体类抗炎镇痛药只能够控制患者的疼痛症状，抑制病情发展，但无法根治疾病，且每日服用会引起骨髓抑制，产生毒副作用[11]，国外研究表明长期使用 MTX 会导致淋巴瘤等恶性肿瘤的发生率升高[12]。LEF 主要通过抑制嘧啶的从头合成途径和酪氨酸激酶的活性发挥作用，对多种自身免疫性疾病和免疫介导性疾病有确切的疗效和良好的安全性，现运用于类风湿疾病[13-15]。LEF 治疗 RA 的不良反应较为少见，且症状轻微。PDN 自身对类风湿也有一定治疗效果，作为一种肾上腺皮质激素类药，具有抗炎、抗过敏、抗风湿、免疫抑制作用，作用机理为抗炎作用，但剂量过大会导致严重不良反应，所以通常使用最小有效剂量治疗 RA[16-18]。临床上将两种药物协同使用，不仅能提高疗效，同时并未提高不良反应的发生率。实验结果表明 MTX 联合 PDN 和 LEF 联合 PDN 药效差异不打，所以临床可根据不同患者对药效敏感度进行选择性使用[19,20]。

综上所述，MTX 联合 PDN 组较纯 MTX 组疗效更好，同时 LEF 联合 PDN 较纯 LEDF 组疗效更好，药物联合使用在提高疗效的同时也保证了药效的安全性，但两种组合疗效差异并不明显，临床可根据不同疾病类型选用不同组合药物。

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