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在线全文

*CYP3A5*基因多态性对狼疮肾炎患者他克莫司血药浓度的影响及与预后的关系

魏 玲[1]，王 涛[2]，胡永梅[1]，谢其冰[3△]

1. 西藏自治区人民政府驻成都办事处医院 全科医学科（成都 610041）；2. 西藏自治区人民政府驻成都办事处医院 老年医学科（成都 610041）；3. 四川大学华西医院 风湿免疫科（成都 610041）

【摘要】 目的 通过研究细胞色素P450（CYP）3A5基因多态性对狼疮肾炎（lupus nephritis，LN）患者他克莫司（tacrolimus，TAC）血药浓度的影响，探索不同基因型LN患者适宜的起始剂量及达到临床缓解的时间差异，并分析影响LN预后的相关因素。**方法** 招募四川大学华西医院风湿免疫科门诊就诊的狼疮肾炎活动期患者，测定患者*CYP3A5*基因型。根据基因型的不同分为AA+GA（快代谢组，基因型为*CYP3A5**1/*1，即AA+*CYP3A5**1/*3）、GG（慢代谢组，基因型为*CYP3A5**3/*3）两组，收集每组患者的基本信息、临床表现、有无其他疾病史及用药史。每种基因型组内按照简单随机分组的原则分为两个起始剂量组，分别给予TAC 0.05 mg/（kg·d）或0.075 mg/（kg·d）起始剂量治疗。每月收集各组包括TAC血药浓度在内的实验室检查指标，血压等相关临床随访指标。每月评估患者是否达到临床缓解，若0.05 mg/（kg·d）起始组治疗2个月后未达到临床缓解者，则增加剂量至0.075 mg/（kg·d）继续观察至第6个月；0.075 mg/（kg·d）起始组治疗期间无论是否达到临床缓解，均持续随访6个月。**结果** 在同一TAC起始剂量组中，GG基因型LN患者的累积缓解率均高于AA+GA基因型患者，但只有0.05 mg/（kg·d）起始剂量组中，两基因型累积缓解率差异有统计性学意义（*P*<0.05）；对比同一基因型的不同TAC起始剂量，0.075 mg/（kg·d）患者缓解率均高于0.05 mg/（kg·d）起始组，但只有AA+GA基因型患者中两起始剂量组缓解率差异具有统计学意义（*P*<0.05）。无论是同一TAC起始剂量组中不同基因型，还是同一基因型的不同TAC起始剂量，患者达到完全缓解时间差异均无统计学意义（*P*>0.05）。无论TAC起始剂量如何，在整个治疗过程中，GG基因型患者TAC血药浓度高于AA+GA基因型。治疗期间的TAC血药浓度（OR=1.941，95%CI 1.47～2.563，*P*<0.001），*CYP3A5**1基因型（OR=0.161，95%CI 0.053～0.492，*P*=0.001），TAC起始剂量（OR=0.205，95%CI 0.113～0.371，*P*<0.001）均能影响患者疗效，TAC血药浓度越大，GG基因型和起始剂量为0.075 mg/（kg·d）的患者达到临床缓解的概率更大。同一基因型不同起始剂量组的不良反应发生率差异均无统计学意义（*P*>0.05）。**结论** TAC治疗LN患者的疗效与*CYP3A5*基因型、TAC血药浓度、TAC起始剂量相关。TAC的血药浓度受*CYP3A5*基因型的影响，慢代谢组TAC血药浓度高于快代谢组，在TAC血药浓度达到6～10 ng/mL时，LN患者更易达到临床缓解。

【关键词】 狼疮肾炎 他克莫司血药浓度 *CYP3A5*基因多态性

Effect of *CYP3A5* Genetic Polymorphisms on the Blood Drug Concentration of Tacrolimus in Patients With Lupus Nephritis and the Relationship With Patient Prognosis

WEI Ling[1], *WANG Tao*[2], *HU Yongmei*[1], *XIE Qibing*[3△]. 1. *Department of General Practice, Hospital of Chengdu Office of People's Government of Xizang Autonomous Region, Chengdu 610041, China*; 2. *Department of Geriatrics, Hospital of Chengdu Office of People's Government of Xizang Autonomous Region, Chengdu 610041, China*; 3. *Department of Rheumatology and Immunology, West China Hospital, Sichuan University, Chengdu 610041, China*

△ Corresponding author, E-mail: xieqibing1971@163.com

[Abstract] Objective To evaluate the effect of cytochrome P450 3A5 (*CYP3A5*) genetic polymorphism on the blood drug concentration of tacrolimus (TAC) in patients with lupus nephritis (LN), to determine the appropriate initial dose for LN patients of different genotypes and the differences in time to remission, and to analyze factors associated with LN prognosis. **Methods** Patients with active LN attending the outpatient clinic of the Department of Rheumatology and Immunology, West China Hospital, Sichuan University were enrolled. Their *CYP3A5* genotypes were determined. According to the different genotypes, the patients were assigned to two groups, the AA + GA group, or the rapid metabolism group with the genotype *CYP3A5**1/*1, i.e., AA + *CYP3A5**1/*3, and the GG group, or the slow metabolism group with the genotype *CYP3A5**3/*3. The basic information, clinical manifestations, history of other diseases, and

△ 通信作者，E-mail: xieqibing1971@163.com

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medication history of the enrolled patients were collected. According to the principle of simple random grouping, patients in each group were randomly divided into two subgroups, receiving TAC at initial doses of 0.05 mg/(kg·d) and 0.075 mg/(kg·d), respectively. Data on laboratory test indicators, including TAC blood drug concentration, blood pressure, and other relevant clinical follow-up indicators, were collected each month from each group. Patients were also evaluated each month for their clinical remission status. When patients in the 0.05 mg/(kg·d) initial dose group did not achieve clinical remission after 2 months, the TAC dose was increased to 0.075 mg/(kg·d), and the patients were observed until the end of the 6th month. Patients in the 0.075 mg/(kg·d) initial dose group were observed for 6 months, regardless of their remission status. **Results** In the LN patient subgroups receiving TAC at the same initial dose, the cumulative remission rate of patients with the GG genotype was higher than that of patients with the AA+GA genotype, but only in the 0.05 mg/(kg·d) initial dose group, the difference in cumulative remission rate between the two genotypes was statistically significant (P < 0.05). According to a comparison of patients with the same genotype who received TAC at different initial doses, the remission rate of patients receiving 0.075 mg/(kg·d) initial dose was higher than that of the 0.05 mg/(kg·d) initial dose group, but only in patients with AA + GA genotype, the difference in remission rate between the two initial dose groups was statistically significant (P < 0.05). Whether it was different genotypes in the same TAC initial dose group or different TAC initial doses of the same genotype, there was no statistically significant difference in the time to achieve complete remission (P > 0.05). Regardless of the different initial TAC doses, patients with the GG genotype maintained higher TAC blood concentrations than those with the AA + GA genotype throughout the course of treatment. TAC blood concentration during treatment (OR = 1.941; 95% CI, 1.47-2.563; P < 0.001), *CYP3A5**1 genotype carrier status (OR = 0.161; 95% CI, 0.053-0.492; P = 0.001), and the initial TAC dose (OR = 0.205; 95% CI, 0.113-0.371; P < 0.001) were all significant factors influencing treatment efficacy. When TAC blood concentration was higher, patients with the GG genotype receiving TAC at an initial dose of 0.075 mg/(kg·d) were more likely to achieve clinical remission. There were no statistically significant differences in the incidence of adverse reactions between subgroups with the same genotype but receiving TAC at different initial doses (P > 0.05). **Conclusion** The efficacy of TAC in treating LN patients is correlated with *CYP3A5* genotypes, TAC blood drug concentration, and TAC initial dose. The blood drug concentration of TAC is influenced by *CYP3A5* genotypes, with the TAC blood drug concentrations of the slow metabolism group being higher than that of the fast metabolism group. When the TAC blood drug concentration reaches 6-10 ng/mL, it is more likely for LN patients to achieve clinical remission.

[Key words] Lupus nephritis Tacrolimus blood drug concentration *CYP3A5* gene polymorphism

狼疮肾炎(lupus nephritis, LN)是系统性红斑狼疮所导致的常见器官损害疾病之一[1], 是免疫复合物沉积于肾脏所致的一种肾炎, 目前仍是SLE的主要死亡原因[2]。他克莫司(tacrolimus, TAC)作为钙调蛋白磷酸酶抑制剂(calcineurin inhibitor, CNI)的代表药物之一[3-6], 被用于LN的治疗疗效确切, 不仅能控制狼疮活动, 而且在迅速减少尿蛋白方面表现优异[7-8]。虽然TAC具有较好的疗效和较低的不良反应, 但是该药具有治疗窗狭窄、药代动力学个体差异性大等特点[9]。因此评估该药的最佳起始剂量、尽快达到LN疾病缓解具有很大的临床意义。

目前国内外多篇文献报道编码细胞色素氧化酶P450(CYP)3A家族的基因位点对于TAC体内的代谢影响最为重要[10-13], 在黄种人群中*CYP3A5*的基因多态性对TAC血药浓度影响最大[14-16]。

因此, 本研究通过前瞻性队列研究, 分析*CYP3A5*的基因多态性对LN患者体内TAC血药浓度的影响以及该基因与LN治疗预后关系, 探求不同*CYP3A5*基因型患者使用TAC治疗适宜的起始剂量, 求证TAC血药浓度是否对疗效存在影响, 为LN患者使用TAC治疗提供更多的参考依据。

1 资料与方法

1.1 一般资料及分组

本研究共纳入2020年12月–2023年2月到四川大学华西医院风湿免疫科门诊就诊的LN患者156例, 符合2012年ACR和EULAR诊断标准[17]的LN活动期患者共103例。其中男女比例1∶6.35, 年龄(36.77±11.01)岁, 病程为(7.40±5.73)年。本研究已通过四川大学华西医院生物医学伦理委员会的审查(批件号: 2019年审1026号), 并签署患者知情同意书。

根据患者基因型分为快代谢(AA+GA组, 基因型为*CYP3A5**1/*1, 即AA+*CYP3A5**1/*3)、慢代谢(GG组, 基因型为*CYP3A5**3/*3)两组[18], 每组内为两个亚组, 分别给予TAC 0.05 mg/(kg·d)或0.075 mg/(kg·d)剂量起始治疗。

排除标准: 对研究用药有严重不良反应患者; 严重肝、肾功能不全(肝酶超过正常上限2倍, 血肌酐超过正常值20%或eGFR<40 mL/(min·1.73 m^2); 同时用CYP3A酶抑

制剂或诱导剂(如大环内酯类药物、抗癫痫药、抗真菌药、抗结核药)等会对TAC血药浓度有明显影响药物的患者; 试验前1个月内已经接受过霉酚酸酯、环磷酰胺、环孢素治疗的患者; 合并其他重要器官系统疾病(如冠心病)或自身免疫疾病的患者; 受孕或不愿使用避孕措施的患者。

1.2　基因型检测

用一次性含乙二胺四乙酸抗凝剂(ethylene diamine ietraacetic acid, EDTA)的紫头真空抽血管采集患者静脉全血2 mL(无须空腹)。应用高通量单核苷酸基因多态性检测技术, 提取检测DNA。*CYP3A5*基因1/3多态性检测采用液相数字荧光分子杂交SNP基因分型方法[19]。

1.3　TAC全血浓度检测

在每次服用TAC前半小时以内, 以一次性EDTA紫头真空抽血管抽取患者空腹静脉血2 mL, 加用样本预处理试剂, 充分混匀为完全溶血混合液, 离心后取上清液, 上机采用电化学发光免疫法(electrochemiluminescence immunoassay, ECLIA)检测。

1.4　治疗方案及随访

本研究按照常规临床实践的方式进行随访, 每月随访1次, 共随访6个月。若0.05 mg/(kg·d)起始组治疗至第2个月未达完全缓解者, 则加量至0.075 mg/(kg·d), 持续治疗并随访至第6个月; 0.075 mg/(kg·d)起始组不论期间是否缓解均持续治疗并随访至第6个月。

1.5　观察指标

每月随访临床指标(体质量、感染、血压、震颤、头痛、失眠、视力、便秘、腹泻、恶心、新发高血压、新发糖尿病、感冒、皮疹等不良反应的发生率)、实验室检查指标(TAC血药浓度、肝肾功、血脂、血糖、电解质、eGFR、血常规、尿常规、24 h尿蛋白定量、补体C3、补体C4), 并行SLEDAI评分。主要终点: LN完全缓解。完全缓解(complete remission, CR)的标准是: 尿蛋白<0.5 g/24 h或尿蛋白/肌酐<50 mg/mmol, 患者肾功能正常或趋于正常[20]。达到完全缓解的时间最好不要超过治疗开始后6个月, 最晚不能超过1年。

1.6　统计学方法

采用SPSS 27.0软件进行统计学分析。本次对于不同分组的累积缓解率的比较采用Kaplan-Meier生存分析。采用方差分析, 得出TAC血药浓度在不同基因型、不同起始剂量下的变化趋势。采用多因素logistic回归分析基因型、TAC血药浓度和起始剂量对疗效的影响。最后对不同TAC起始剂量的不良反应发生率采用卡方检验进行对比。绘图软件为GraphPad 10.0。P<0.05为差异有统计学意义。

2　结果

2.1　分组及基线情况

AA+GA组(n=50)中女性43例, 男性7例, 年龄(37.18±11.51)岁; 0.05 mg/kg/d起始组35例, 0.075 mg/kg/d起始组15例。GG组(n=53)中女性46例, 男性7例, 年龄(36.38±10.62)岁, 0.05 mg/(kg·d)起始组31人, 0.075 mg/(kg·d)起始组22例, 各组患者基线特征均衡, 差异均无统计学意义。见表1、表2。

表 1　快代谢组和慢代谢组基线情况

Table 1　Baseline data of the fast metabolism group and the slow metabolism group

Variable	Total (n = 103)	AA + GA (n = 50)	GG (n = 53)	P
Female/case (%)	89 (86.4)	43 (86.0)	46 (86.8)	0.907
Age/yr.	36.77 ± 11.01	37.18 ± 11.51	36.38 ± 10.62	0.714
Body mass/kg	53.95 ± 9.51	54.46 ± 8.97	53.47 ± 10.05	0.600
Course of disease/years	7.40 ± 5.73	7.20 ± 6.02	7.59 ± 5.49	0.732
Urine protein (g/24 h)	1.56 ± 1.04	1.53 ± 1.14	1.59 ± 0.94	0.751
Prednisone/(mg/d)	12.09 ± 9.35	13.05 ± 10.29	11.18 ± 8.36	0.313
HCQ/case (%)	94 (91.3)	45 (90.0)	49 (92.5)	0.660

HCQ: hydroxychloroquine.

表 2　0.05 mg/(kg·d)起始组和0.075 mg/(kg·d)起始组基线情况

Table 2　Baseline data of the 0.05 mg/(kg·d) initial dose group and the 0.075 mg/(kg·d) initial dose group

Variable	Total (n = 103)	0.05 mg/(kg·d) (n = 66)	0.075 mg/(kg·d) (n = 37)	P
Female/case (%)	89 (86.4)	58 (87.9)	31 (83.8)	0.561
Age/yr.	36.77 ± 11.01	37.62 ± 11.56	35.24 ± 9.94	0.295
Body mass/kg	53.95 ± 9.51	54.59 ± 9.17	53.31 ± 9.92	0.601
Course of disease/years	7.40 ± 5.73	7.55 ± 5.95	7.13 ± 5.38	0.724
Urine protein/(g/24 h)	1.56 ± 1.04	1.62 ± 0.96	1.50 ± 1.12	0.747
Prednisone/(mg/d)	12.09 ± 9.35	12.25 ± 8.95	11.79 ± 10.15	0.811
HCQ/case (%)	94 (91.3)	60 (91.0)	34 (91.9)	0.865

HCQ: hydroxychloroquine.

2.2　各组缓解情况比较

2.2.1　同一TAC起始剂量的不同基因型LN患者的缓解情况

见图1、表3及图2。对同一TAC起始剂量的不同基因型LN患者的缓解情况进行分析发现: 以0.05 mg/(kg·d)剂量起始, GG组的完全缓解率高于与AA+GA组(P<0.05), 但两种基因型患者到达缓解的时间差异无统计学意义; 以0.075 mg/(kg·d)剂量起始, GG组的完全缓解率高于AA+GA基因型, 但差异无统计学意义, 两种基因型患者达到缓解的时间差异也无统计学意义。

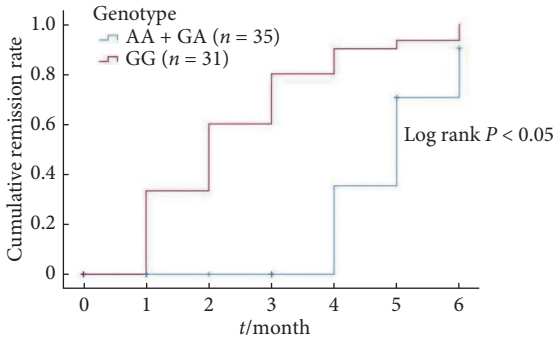

图 1 0.05 mg/（kg·d）剂量起始的不同基因型LN患者的累积缓解率

Fig 1 Cumulative remission rates in lupus nephritis patients of different genotypes treated with an initial dose of 0.05 mg/(kg·d)

表 3 同一起始剂量组的不同基因型LN患者临床缓解情况

Table 3 Remission for lupus nephritis patients with different genotypes treated with the same initial dose

Initial dose	Genotype	*n*	CR/case (%)	Time to CR/month, median (P_{25}, P_{75})
0.05 mg/(kg·d)	AA + GA	35	14 (40.0)*	3.0 (1.0, 5.0)
	GG	31	30 (96.8)	3.0 (1.0, 3.0)
	Total	66	44 (66.7)	3.0 (1.0, 4.0)
0.075 mg/(kg·d)	AA + GA	15	12 (80.0)	3.0 (2.0, 4.5)
	GG	22	22 (100.0)	2.0 (2.0, 3.0)
	Total	37	34 (91.9)	2.0 (2.0, 3.0)

CR: complete remission. * $P < 0.05$, vs. GG genotype treated with the same initial dose.

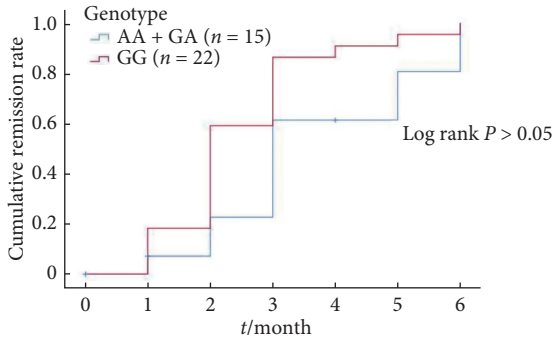

图 2 0.075 mg/（kg·d）剂量起始的不同基因型LN患者的累积缓解率

Fig 2 Cumulative remission rates in lupus nephritis patients with different genotypes treated with an initial dose of 0.075 mg/(kg·d)

2.2.2 同一基因型LN患者的不同起始剂量的缓解情况

比较同一基因型LN患者采用不同起始剂量时的缓解情况发现: AA+GA基因型患者中, 起始剂量为0.075 mg/(kg·d)的患者缓解率高于起始剂量为0.05 mg/(kg·d)的患者(P<0.05), 但达到缓解的时间差异无统计学意义(图3及表4)。GG基因型患者中, 起始剂量0.05 mg/(kg·d)和0.075 mg/(kg·d)患者的缓解率和缓解时间差异均无统计学意义(图4及表4)。

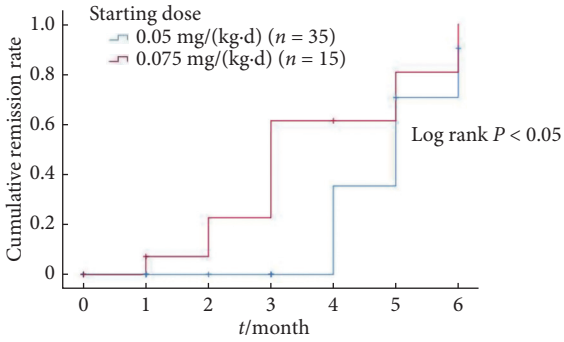

图 3 不同TAC起始剂量AA+GA基因型LN患者的累积缓解率

Fig 3 Cumulative remission rates in lupus nephritis patients of the AA+GA genotype treated with different starting doses

表 4 同一基因型LN患者使用不同起始剂量临床缓解情况

Table 4 Remission for lupus nephritis patients with the same genotype treated at different initial doses

Genotype	Initial dose	*n*	CR/case (%)	Time to CR/month, median (P_{25}, P_{75})
AA + GA	0.05 mg/(kg·d)	35	14 (40.0)*	3.0 (1.0, 5.0)
	0.075 mg/(kg·d)	15	12 (80.0)	3.0 (2.0, 4.5)
	Total	50	26 (52.0)	3.0 (1.0, 5.0)
GG	0.05 mg/(kg·d)	31	30 (96.8)	2.0 (1.0, 3.0)
	0.075 mg/(kg·d)	22	22 (100.0)	2.0 (2.0, 3.0)
	Total	53	52 (98.1)	2.0 (1.0, 3.0)

CR: complete remission. * $P < 0.05$, vs. the same genotype treated at 0.075 mg/(kg·d).

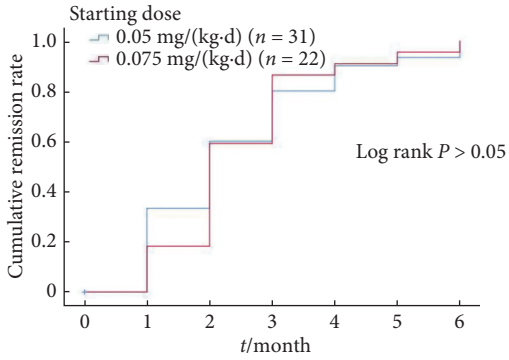

图 4 GG基因型LN患者不同起始剂量的累积缓解率

Fig 4 Cumulative remission rates in lupus nephritis patients of the GG genotype treated with different starting doses

2.3 TAC血药浓度的变化

在整个随访期间, 无论TAC起始剂量如何, GG基因型LA患者体内TAC血药浓度均显著高于AA+GA基因型LA患者; 在每个时点下, GG基因型内0.075 mg/(kg·d)剂量的TAC血药浓度均高于0.05 mg/(kg·d)剂量; 而AA+GA基因型只有在随访第4、5个月时, 0.05 mg/(kg·d)和0.075 mg/(kg·d)剂量的TAC血药浓度差异有统计学意义, 其余4个月差异不显著。而在同一个组内, TAC血药浓度随时间增加均呈现升高的趋势(图5)。

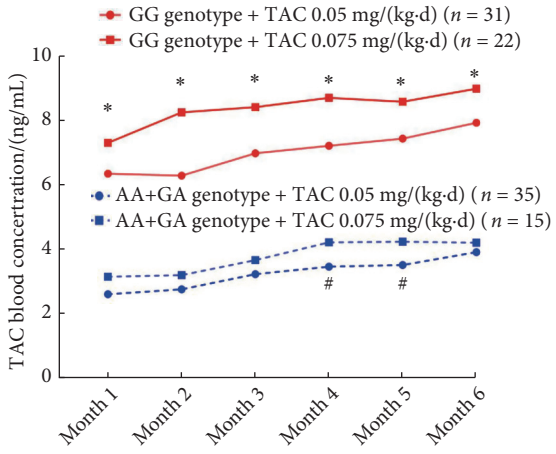

图 5 TAC血药浓度变化趋势图

Fig 5 The trend of TAC blood concentration

* $P < 0.05$, GG genotype + TAC 0.05 mg/(kg·d) vs. GG genotype + TAC 0.075 mg/(kg·d); # $P < 0.05$, AA+GA genotype + TAC 0.05 mg/(kg·d) vs. AA+GA genotype + TAC 0.075 mg/(kg·d).

2.4 TAC血药浓度对疗效的影响

多因素logistic回归分析(表5)提示: 在治疗过程中TAC血药浓度越大, 患者达到临床缓解的概率越大(OR=1.941, 95%CI 1.47 ~ 2.563, *P*<0.001)。AA+GA基因型患者出现缓解的概率比GG基因型患者要低(OR=0.161, 95%CI 0.053 ~ 0.492, *P*=0.001)。TAC起始剂量为0.05 mg(kg·d)的患者达到临床缓解的概率低于起始剂量为0.075 mg/(kg·d)的患者(OR=0.205, 95%CI 0.113 ~ 0.371, *P*<0.001)。治疗时间对是否达到临床缓解影响不显著(*P*>0.05)。

2.5 不良反应发生率

通过对同一基因型患者不同起始剂量的不良反应发生率进行分析, 结果(表6)提示: AA+GA基因型起始剂量为0.05 mg/kg/d的患者中出现肾功能进展1例(2.9%), 血脂升高4例(11.4%), 血压升高4例(11.4%), 临床随访出

表 5　不同临床因素对LN患者疗效的影响

Table 5　Effect of TAC blood concentrations on the efficacy

Parameter		β	Wald Chi-Square	*P*	OR (95% CI)
(Intercept)		0.382	0.12	0.729	1.466 (0.168-12.774)
TAC blood concentration		0.663	21.861	< 0.001	1.941 (1.47-2.563)
Genotype	AA + GA	−1.825	10.286	0.001	0.161 (0.053-0.492)
	GG	0	—	—	1
Starting dose/(mg/[kg·d])	0.05	−1.586	27.46	< 0.001	0.205 (0.113-0.371)
	0.075	0	—	—	1
Time	Month 1	0.884	3.655	0.056	2.421 (0.978-5.995)
	Month 2	0.79	3.109	0.078	2.204 (0.916-5.303)
	Month 3	0.447	1.098	0.295	1.564 (0.677-3.613)
	Month 4	0.246	0.318	0.573	1.279 (0.544-3.006)
	Month 5	0.193	0.191	0.662	1.213 (0.511-2.881)
	Month 6	0	—	—	1

OR: odds ratio.

表 6　同一基因型LN患者TAC不同起始剂量的不良反应发生率

Table 6　Incidence of adverse reactions to different starting doses of TAC in lupus nephritis patients of the same genotype

Index		AA + GA genotype		GG genotype	
		0.05 mg/(kg·d) (*n* = 35)	0.075 mg/(kg·d) (*n* = 15)	0.05 mg/(kg·d) (*n* = 31)	0.075 mg/(kg·d) (*n* = 22)
Cr	Normal	34 (97.1%)	14 (93.3%)	31 (100%)	22 (100%)
	Abnormal	1 (2.9%)	1 (6.7%)	—	—
LFTs	Normal	35 (100%)	15 (100%)	31 (100%)	22 (100%)
	Abnormal	—	—	—	—
Glucose	Normal	35 (100%)	14 (93.3%)	28 (90.3%)	22 (100%)
	Abnormal	0 (0%)	1 (6.7%)	3 (9.7%)	0 (0%)
CBC	Normal	35 (100%)	15 (100%)	29 (93.5%)	20 (90.9%)
	Abnormal	—	—	2 (6.5%)	2 (9.1%)
Lipid profile	Normal	31 (88.6%)	15 (100%)	30 (96.8%)	22 (100%)
	Abnormal	4 (11.4%)	0 (0%)	1 (3.2%)	0 (0%)
BP	Normal	31 (88.6%)	15 (100%)	28 (90.3%)	22 (100%)
	Abnormal	4 (11.4%)	0 (0%)	3 (9.7%)	0 (0%)

Cr: creatinine; LFTs: liver function tests; Glucose: blood glucose; CBC: complete blood count; BP: blood pressure.

现视物模糊、手抖不良反应共2例(5.7%);起始剂量为0.075 mg/kg/d的患者中出现肾功能进展1例(6.7%),血糖升高1例(6.7%),不同起始剂量两组间各种不良反应率差异均无统计学意义(P>0.05)。GG基因型起始剂量为0.05 mg/kg/d的患者中出现血糖升高3例(9.7%),白细胞减少2例(6.5%),血脂升高1例(3.2%),血压升高3例(9.7%),临床随访出现过敏、头昏、头痛不良反应共3例(9.7%);起始剂量为0.075 mg/kg/d的患者中出现白细胞减少2例(9.1%),不同起始剂量两组间各种不良反应率差异均无统计学意义(P>0.05)。

3 讨论

TAC作为一种新型的强效免疫抑制剂,不仅用于移植患者改善移植器官的存活率,而且在自身免疫病的治疗中应用也日趋广泛,国内外权威指南均推荐TAC可作为LN诱导缓解治疗的主要药物之一[21]。目前国内外关于*CYP3A5*基因多态性对TAC血药浓度影响的研究主要集中在器官移植患者,LN中尚未见文献报道,导致目前TAC治疗LN时缺乏统一的标准,临床用药无章可循。因此拟通过该项研究探索*CYP3A5*基因多态性对LN患者TAC血药浓度的影响及与LN预后的关系。

本研究将符合纳入标准的103例LN患者根据其基因型分为快代谢、慢代谢两组[22-24],每一组内再根据TAC起始剂量的不同分为两个亚组。通过6个月的治疗和随访,进行临床疗效、安全性评价,得到以下结论。

首先,通过对比同一起始剂量的不同基因型LN患者的缓解率,提示不论是以0.05 mg/(kg·d)剂量起始还是以0.075 mg/(kg·d)剂量起始,GG基因型患者的缓解率均高于AA+GA基因型患者。可以得出:*CYP3A5*基因多态性会显著影响缓解率,慢代谢组缓解率明显高于快代谢组。

其次,通过对比同一基因型的不同起始剂量LN患者的缓解率,提示AA+GA基因型患者中,起始剂量为0.075 mg/(kg·d)的患者缓解率显著高于起始剂量为0.05 mg/(kg·d)的患者(P<0.05);GG基因型患者中,起始剂量0.05 mg/(kg·d)和0.075 mg/(kg·d)患者的缓解率差异无统计学意义(P>0.05)。我们推测,在快代谢组中,加大起始剂量会提高缓解率,然而在慢代谢组中,由于TAC的蓄积,小剂量起始即可达到较高缓解率,加大剂量缓解率差异不明显。

再次,通过分析TAC血药浓度在不同基因型、不同起始剂量下的变化趋势,提示GG基因型患者整体的TAC血药浓度6 ~ 10 ng/mL,显著高于AA+GA基因型患者的TAC血药浓度2 ~ 4 ng/mL。结合前面结论,GG基因型的LN患者的缓解率高于AA+GA基因型患者,可以推断:在TAC达到有效血药浓度(6 ~ 10 ng/mL)时,LN患者更易达到临床缓解。这一结论也验证了《他克莫司在狼疮肾炎中应用的中国专家共识》中所提示的相关内容[7],即在诱导缓解时TAC谷浓度应维持在6 ~ 10 ng/mL。2015年一项由中国26个肾脏病中心参与的多靶点(TAC 4 mg/d联合MMF 1.0 g/d)治疗Ⅲ、Ⅳ、Ⅴ及混合型LN的研究[25]显示有16.5%的患者随访6个月无缓解。但该项研究并未充分地考虑到*CYP3A5*的基因多态性对TAC血药浓度将会产生影响,对所有患者均统一使用TAC 4 mg/d的剂量,可能出现*CYP3A5**1表达者TAC血药浓度过低而难以达到临床缓解。因此,维持有效血药浓度,是发挥TAC治疗作用的关键。

同时,我们也关注了TAC用药的安全性。在既往对于TAC血药浓度的研究中,认为TAC血药浓度过高,可能引起肾毒性或增加感染风险[26-27]。和其他钙调磷酸酶抑制剂(如环孢素)一样,TAC在高剂量使用时可引起急性或慢性肾毒性[28]。这将会出现一系列的病理生理表现,如肾血流量及肾小球滤过率降低,肾血管阻力的增加;相关性指标的升高,如血清、肾皮质丙二醛、血肌酐以及血清尿素氮等[29]。在本研究中,我们未发现基因型和TAC起始剂量与不良反应率有关系(P>0.05)。这可能与该研究中TAC以中小剂量起始,并未一开始就使用0.1 mg/(kg·d)的极量,且TAC血药浓度多控制在10 ng/mL以内、随访时间短有关。

当然,在该研究中也存在一些不足,如研究的样本量稍有欠缺,由于AA基因型在中国人群很少见,所以无法独立成组进行统计分析;本研究未剔除其他基因SNP连锁不平衡对TAC血药浓度的影响;另外,该研究随访时间偏短,对TAC血药浓度长期波动趋势及远期不良反应的研究不足。

综上所述,LN患者在选择TAC治疗时,其疗效与*CYP3A5*基因型、TAC血药浓度、TAC起始剂量相关。*CYP3A5*基因型对TAC的血药浓度存在影响,慢代谢组(*CYP3A5**3/*3)TAC血药浓度均高于快代谢组(*CYP3A5**1/*1、*CYP3A5**1/*3),在TAC血药浓度达到6~10 ng/mL时,LN患者更易达到临床缓解。快代谢组中TAC以中等剂量0.075 mg/(kg·d)起始更合适,慢代谢组中TAC以小剂量0.05 mg/(kg·d)起始即可。

* * *

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