

· 综 述 ·

治疗药物监测在西罗莫司用于儿童期脉管异常中的研究进展

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[摘要] 西罗莫司(sirolimus, SRL)近年来被广泛应用于治疗脉管异常疾病。由于其治疗窗狭窄,药代动力学参数存在较大的个体内和个体间变异性,需要常规进行治疗药物监测以确保疗效和避免不良反应。因此,本文回顾了SRL的血药浓度监测方法以及不同检测方法之间的对比研究,并讨论SRL在脉管异常群体中应维持的浓度范围。SRL浓度检测方法包括免疫法和色谱法两类,免疫法与色谱法相比存在显著的阳性偏倚,液相色谱串联质谱法是大多数实验室采用的“金标准”方法。SRL的目标血药浓度范围多为5~15 ng/mL或10~15 ng/mL。但脉管异常疾病存在多个分类,SRL在该疾病的临床应用情况较为复杂,治疗药物监测也无可供参考的指南。未来需进一步研究,以获取更多高级别的循证医学证据来指导SRL的治疗性监测及个体化用药。

[关键词] 西罗莫司;脉管异常;治疗药物监测;血药浓度

[中图分类号] R725.4

[文献标志码] A

[文章编号] 1007-4368(2023)09-1319-05

doi:10.7655/NYDXBNS20230922

Recent advances in therapeutic drug monitoring of sirolimus in the treatment of childhood vascular anomalies

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[Abstract] Sirolimus (SRL) has been widely used to treat vascular anomalies in recent years. The routine therapeutic drug monitoring for SRL is required to ensure efficacy and prevent adverse effects, due to its narrow therapeutic window and large intra- and inter-individual variability in pharmacokinetics. This article reviewed the analytical methods for SRL blood concentration and the comparison studies between different assays, and discussed the target blood concentration range of SRL in vascular anomalies. The analytical methods for determination of SRL include immunoassays and liquid chromatography-based methods. Immunoassays exhibit significant positive bias, compared to chromatography. Liquid chromatography tandem mass spectrometry is regarded as the “gold standard” in most clinical labs. Generally, goal SRL blood concentrations maintain at 5–15 ng/mL or 10–15 ng/mL. However, there are several classifications of vascular anomalies, and treatment of SRL in these diseases is complicated, and no guidelines for the implementation of therapeutic drug monitoring can be adhered. Future investigations are needed to obtain a more high-level evidence-based medical evidence to guide the therapeutic monitoring and individualized medication of SRL.

[Key words] sirolimus; vascular anomalies; therapeutic drug monitoring; blood concentration of drug

[J Nanjing Med Univ, 2023, 43(09): 1319-1323]

[基金项目] 江苏省卫生健康委员会特聘医学专家项目(2019)

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西罗莫司(sirolimus, SRL)是一种特异性的哺乳动物雷帕霉素靶蛋白抑制剂,能阻断下游蛋白合成和随后的细胞增殖及血管生成^[1]。近年来,SRL在脉管异常(vascular anomalies, VA)中的应用逐渐得到广泛认可,且在大多数研究中表现出良好的疗效和安全性^[2-4]。2022年意大利VA研究学会发布的指南中推荐SRL用于治疗复杂或进展的卡波西型血管内皮瘤和丛状血管瘤(证据等级为2+)以及蓝色橡皮瘁样痣综合征(证据等级为1++)^[5]。中华医学会发布的2019版血管瘤和脉管畸形的诊断及治疗指南中也提出SRL作为卡波西型血管内皮瘤和丛状血管瘤的一线用药^[6]。

但是,SRL的药物代谢动力学在用药人群中表现出较大的个体间和个体内变异性,且存在潜在的药物-药物相互作用风险和不服从情况,儿童期的生理学特征使这一问题变得更为复杂^[7-8]。因此,实施主动的治疗药物监测(therapeutic drug monitoring, TDM)可以发挥积极的辅助治疗作用^[9-11]。

本文从SRL的药物代谢动力学出发,围绕TDM,总结和分析监测SRL浓度的方法,并重点讨论儿科患者的目标血药浓度范围。

1 药物代谢动力学

SRL口服给药后迅速吸收,平均达峰时间为1~2 h,但生物利用度低,约为15%。SRL具有较大的表观分布容积,可达 (12 ± 5) L/kg,在体内约95%与红细胞结合^[12]。SRL在肠道和肝脏中主要经细胞色素P450酶3A4和3A5催化代谢为各种去甲基化和羟基化产物,其活性均小于母药的10%,包括39-O-去甲基西罗莫司、12-O-羟基西罗莫司和34-O-羟基西罗莫司等^[13]。此外,SRL也是肠道中外排蛋白P-糖蛋白的底物。SRL的平均消除半衰期长达60 h,胆汁排泄是SRL的主要排泄途径^[14]。

2 治疗药物监测

2.1 治疗药物监测的必要性

SRL的治疗窗狭窄,美国食品药品监督管理局发布的药品说明书指出,当其用于治疗淋巴管平滑肌瘤时,建议谷浓度维持在5~15 ng/mL^[15]。SRL在药代动力学方面表现出较高的患者内和患者间变异性。MacDonald等^[16]发现,在肾移植患者中,SRL口服清除率在患者内和患者间的变异性分别为26%和52%。同样是在肾移植群体中,Kahan等^[17]研究指出,SRL谷浓度在患者内的变异性为

72.6%,在患者间的变异性为54.8%。SRL的血药浓度与疗效和不良反应均密切相关。在既往研究中,SRL谷浓度<5 ng/mL与肾移植后急性排斥反应的发生和严重程度之间存在显著相关性,谷浓度>15 ng/mL则与出现高甘油三酯血症、血小板减少症和白细胞减少症等不良反应有关^[17]。此外,年龄、种族、饮食、疾病状态、药物相互作用以及药物代谢酶和转运体的基因多态性等因素都会影响SRL的体内暴露^[18-20]。

以上血药浓度监测数据主要在移植患者人群中获得,在儿童期VA中的研究并不多见。但是,显著的个体内和个体间变异提示对SRL进行TDM是有益的,有助于推动个体化给药的实践以及保证用药时的疗效和安全性^[21]。

2.2 血药浓度检测方法

SRL的谷浓度与它的药-时曲线下面积具有良好的相关性^[16],是一个可用于监测SRL体内暴露的简单而可靠的指标。绝大部分SRL都分布在红细胞中,所以测定其浓度时的首选基质是全血。检测SRL浓度的方法分为两种,一种是免疫分析法,另一种是色谱法。

免疫分析法基于药物(抗原)与特定抗体之间的反应,由此生成的抗原/抗体复合物能够产生可被检测的信号。免疫分析法快速且易于操作,前处理方法通常较为简单,尤其适用于进行常规TDM。用于检测SRL浓度的免疫分析技术主要包括微粒子酶免疫分析法(microparticle enzyme immunoassay, MEIA)、酶联免疫放大法(enzyme multiplied immunoassay technique, EMIT)、化学发光微粒子免疫分析法(chemiluminescent microparticle immunoassay, CMIA)和荧光偏振免疫分析法等^[22]。但是由于生物基质中可能存在干扰成分以及药物代谢物或其他物质与抗体的交叉反应,这种方法的主要问题是会高估SRL浓度^[23]。

色谱法如高效液相色谱法(high performance liquid chromatography, HPLC)、高效液相色谱-质谱法(high performance liquid chromatography - mass spectrometry, HPLC-MS)等的特异性比免疫分析法更高。但当分析物以极低浓度存在于血液样本中时,普通HPLC法难以达到理想的灵敏度。除此以外,普通HPLC法的提取步骤通常比较复杂,检测所需时间较长。

液相色谱-串联质谱法(liquid chromatography tandem mass spectrometry, LC-MS/MS)结合了色谱对

复杂样品的高分离能力和质谱的高选择性、高灵敏度等优势,可以在短时间内分别测定目标待测物及其代谢物,是目前大多数临床实验室测定SRL浓度所采用的“金标准”方法^[24]。已有多种LC-MS/MS方法被开发并用于SRL的TDM^[25-28]。笔者团队也建立了一种简单、快速、灵敏地测定人全血中SRL浓度的LC-MS/MS方法,该方法只需要通过简单的蛋白沉淀进行样品制备,每个样本的运行时间为3 min,线性范围为0.5~50.0 ng/mL,且已日常应用于VA儿科患者的临床TDM实践^[29]。

2.3 不同检测方法之间的对比研究

免疫分析法的性能受到交叉反应和红细胞压积等基质效应的影响,与色谱法相比存在明显的阳性偏倚。检测方法的对比研究主要集中在这两种方法之间。Salm等^[30]的研究纳入接受SRL治疗的肾移植患者的841个谷浓度血液样本,经两种不同方法检测后发现,与HPLC-MS法相比,MEIA法的平均阳性偏倚为42.5%。Morris等^[31]收集了116份来自肾移植患者的全血样本,并采用MEIA法和LC-MS/MS法分别进行检测,数据显示,MEIA法的平均偏差为49.2%。

Johnson-Davis等^[32]对保存在-20℃条件下的不同器官移植的样本进行分析,以评估LC-MS/MS法与CMIA法之间的偏差。结果显示,对于肾移植样本,CMIA的平均阳性偏倚为14.6%。笔者团队进行了LC-MS/MS法与EMIT法测定SRL浓度的对比研究^[29],共纳入49例接受SRL治疗的VA患儿的114个血液样本,结果表明EMIT法测定的结果平均高估了4.7 ng/mL,平均阳性偏倚为63.1%。

在不同方法的对比研究中,免疫分析法在测定浓度时都存在明显的高估现象。尽管有结果上的差异,免疫分析法与色谱法之间仍然具有良好的相关性,说明两种方法之间的切换是可行的。当从免疫分析法切换到色谱法时,TDM实验室需要向临床医师和患者解释浓度下降是由于之前使用的免疫法存在高估现象。同时应该更加关注药物治疗的有效性和安全性,而不仅仅是浓度数据。此外,由于不同分析方法存在检测结果上的差异,当在同一临床实验室内进行方法切换或不同实验室之间进行结果比较时,可能需要对目标治疗参考范围进行必要的重新评估。

2.4 血药浓度参考范围

SRL治疗VA时的使用剂量并不统一,在儿童中最常用的起始剂量为0.8 mg/(m²·12 h)^[33]。SRL在

儿童期VA中的治疗范围最初是基于在肾移植群体中的经验,通常认为5~15 ng/mL或10~15 ng/mL是足够的^[34]。一篇系统综述分析了20项SRL治疗淋巴管畸形的研究,结果显示在纳入的71例患者中,60例患者经SRL治疗后达到部分缓解,SRL的目标范围则大多都维持在5~15 ng/mL或10~15 ng/mL^[35]。Freixo等^[34]进行了一项系统综述,共纳入73项研究,患者分为血管瘤和脉管畸形两组。血管瘤组和脉管畸形组最常用的剂量都为0.8 mg/(m²·12 h),其中血管瘤组的目标血药浓度大多维持在10~15 ng/mL(38.4%)和15~20 ng/mL(24.7%),脉管畸形组的目标血药浓度多数维持在5~15 ng/mL(43.8%)和10~15 ng/mL(33.3%)。此外,该系统综述还指出在儿科患者中,血药浓度的目标范围通常为10~15 ng/mL(38.3%)和5~15 ng/mL(38.3%)。而在其他研究中,较低的SRL浓度对VA患者也是有效的。Erickson等^[36]对2例纤维脂肪脉管异常患者使用SRL治疗,剂量为0.8 mg/(m²·12 h),浓度则维持在2~8 ng/mL,患者的疼痛和生活质量得到快速、显著的改善。

VA可以分为多种类型,每类疾病的发病机制和具体治疗方案存在一定差异,因此TDM的参考浓度范围并不完全相同。一般而言,高剂量SRL(浓度≥8 ng/mL)适用于严重凝血功能障碍、多器官衰竭和危及生命或侵袭性病变的患者,而低、中剂量SRL(浓度<8 ng/mL)则更适合帮助患者缓解症状^[37]。笔者团队曾对SRL在儿童VA患者中的应用情况进行了总结分析,为SRL的合理应用提供了详实的临床进展资料^[38]。

3 结论与展望

本文主要阐述了对SRL进行TDM的必要性、药物浓度的检测方法不同方法之间的对比研究,重点关注SRL应用于VA时的参考浓度范围。SRL治疗期间进行常规TDM是非常必要的,可以维持适宜的药物浓度,确保疗效并避免出现不良反应。目前多数研究采用的目标血药浓度范围为5~15 ng/mL或10~15 ng/mL。但VA较为复杂,存在多个分类,治疗策略也不尽相同,关于SRL在VA中的TDM实践至今还没有统一的共识或指南,仍然需要进行相关研究,以确定针对不同类型VA的药物治疗浓度范围,为临床合理用药提供循证依据。

目前TDM策略采用的是个体剂量调整,以达到目标血药浓度,在个体化治疗方面存在一定局限性。药物遗传学关注遗传多态性对药物治疗结果

的影响,与常规TDM结合可能使初始剂量个体化,并有助于更快实现目标血药浓度。此外,群体药物代谢动力学整合了多种变量对药物暴露的影响,在剂量个体化方面表现出巨大潜力,也是近年来TDM研究的热点。TDM结合药物遗传学和群体药物代谢动力学对于探索SRL在VA中个体化精准用药方案具有重要意义,值得关注。

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[收稿日期] 2023-03-29
(本文编辑:陈汐敏)