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利福昔明治疗肝硬化的研究进展*

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［摘要］ 肝硬化是慢性肝病的一种晚期表现，近年来针对肝硬化的治疗取得了显著进展，以控制症状和并发症发生为主要目标。利福昔明是一种胃肠道吸收极少的抗生素，它可以通过影响肠道微生物群及肠-肝轴等干预肝硬化进程。利福昔明治疗肝硬化及其并发症的疗效得到了越来越多的研究，本文就利福昔明治疗肝硬化的研究进展进行综述，以更好地指导临床用药。

［关键词］ 利福昔明；肝硬化；并发症；肠道微生态；肝肠循环；综述
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Research progress of rifaximin in the treatment of cirrhosis*

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［**Abstract**］ Cirrhosis is an advanced manifestation of chronic liver disease. In recent years, significant progress has been made in the treatment of cirrhosis, with the main goal being to control symptoms and complications. Rifaximin, an antibiotic with minimal gastrointestinal absorption, can interfere with the progression of cirrhosis by affecting the intestinal microbiota and the enterohepatic axis. More and more studies have been conducted on the efficacy of rifaximin in the treatment of cirrhosis and its complications. This article reviewed the research progress of rifaximin in the treatment of cirrhosis, so as to better guide clinical medication.

［**Key words**］ rifaximin; liver cirrhosis; complication; intestinal microecology; hepato-enteral circulation; review

肝硬化是全球面临的日益严峻的医疗挑战之一，各种原因导致的慢性肝病都可以发展为肝硬化，最终导致门静脉高压、腹水、肝性脑病（hepatic encephalopathy，HE）及肺、肾和心脏功能障碍等[1]，严重影响患者预后。肝硬化治疗目前尚缺乏明确的共识，对其有明显影响的干预措施是病因学治疗，然而部分患者仍进一步失代偿，生存质量差、预期寿命缩短[2-3]，因此，有必要采取其他治疗方法。

肝硬化患者肠道细菌过度生长和微生物群组成变化很常见，肠道屏障功能被破坏，通透性增加，内毒素水平升高，可导致细菌移位增加，引起感染、全身炎症反应等；此外，细菌毒素也可直接损伤肝细胞，引起失代偿和器官衰竭[4-5]。利福昔明除了具有直接抗菌作用外，还可以通过调节肠道菌群及其他途径发挥有益作用，从而降低肝硬化患者促炎性因子水平，并提高其抗炎功能[6]，并且减少肠道产氨细菌和肠道细菌移位，从而降低血氨水平及内毒素活性、改善大脑认知[7]。利福昔明对胃肠道微环境的调节似乎对整个肠-肝-脑轴产生积极影响，从而降低肝硬化患者死亡率。本文旨在从利福昔明治疗肝硬化的机制入手，阐述其对肝硬化并发症的治疗作用。

1　利福昔明的药理学特征

利福昔明是一种抗菌范围广、抗菌活性好的非系统性抗生素，它通过结合细菌 DNA 依赖性 RNA 聚合酶发挥抗菌作用，其耐药性低，系统不良事件少，在包括幼儿的患者群体中使用均安全[8-10]。在过去 10 年，多药耐药细菌感染在肝硬化患者中的发生率大幅上升，导致一线抗生素治疗失败及患者预后不良[11]。最近 SHAMSADDINI 等[12]研究也发现，肝硬化患者的抗生素耐药基因负荷较高，并且随着疾病进展而恶化，但与可吸收抗生素不同，利福昔明对抗生素耐药基因有良好的调节作用。利福昔明用于肝硬化患者的治疗越来越受到学界认可，其可以控制症状并减少并发症发生，延缓疾病进展。

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2 利福昔明对肠道微生物群及全身炎症反应的影响

肠道和肝脏通过胆道、门静脉和体循环联通并相互影响，肝硬化患者肠道微生物菌群失调，肠道屏障功能被破坏，微生物及其产物可转移至肝脏引发炎症和损伤，一些易位的肠道产物也可能直接在肝脏发挥作用，从而加剧肝脏疾病[13]。目前证据表明，利福昔明可以减少保护性黏液屏障破坏，并改善肠道微环境，有助于提高抗菌和肠道屏障修复功能，从而减轻肝损伤及全身炎症反应[14-15]。有研究发现，使用利福昔明治疗后，微生物群中双歧杆菌和乳酸杆菌的丰度增加，而粪便杆菌的丰度略有下降，双歧杆菌和乳酸杆菌具有抗炎、免疫调节等作用，提示利福昔明可能通过影响肠道微生物群的结构和功能，改善全身炎症反应[16]。此外，POSE 等[17]最新研究发现，辛伐他汀与利福昔明联合可通过抑制色氨酸-犬尿氨酸途径，减少参与炎症和免疫反应的代谢物产生，同时降低血脂、脂肪酸及次级胆汁酸水平，提示利福昔明可能通过影响代谢途径调节肠道菌群，减少全身炎症反应，这为应用新的肝硬化靶向疗法防止疾病进展奠定了基础。

3 利福昔明对肝纤维化的影响

肝硬化患者肠道通透性增加，内毒素水平升高，内毒素流入肝脏后刺激 Toll 样受体 4（Toll-like receptor 4，TLR4），而 TLR4 作为脂多糖（lipopolysaccharide，LPS）受体，是已知最强的炎症诱导剂之一，对肌成纤维细胞激活和纤维生成具有重要作用；此外，内毒素还可以通过库普弗细胞促进肝星形细胞（hepatic stellate cel，HSC）的激活，并通过 MyD88 依赖性核因子-κB（MyD88-NF-κB）途径提高 HSC 对转化生长因子-β（TGF-β）诱导信号的敏感性，增强 HSC 的激活，诱导肝纤维化[18]。HSC 在肝纤维化过程中具有重要作用，在各种炎症刺激作用下可激活为肌成纤维细胞，这些细胞具有增殖性、收缩性及免疫调节性，并合成过量的细胞外基质，导致细胞基质沉积、肝内炎症和纤维化[19]。

最近一项对酒精性肝病小鼠的研究发现，醋酸锌和利福昔明联合可以通过影响 LPS 和 TLR4/NF-κB 途径抑制炎症反应，减轻肝脏的脂肪变性和纤维化，降低氧化应激，并通过恢复紧密连接蛋白保持肠道屏障的完整性，从而对酒精性肝病相关纤维化起到预防作用[20]。这可能与利福昔明介导的孕烷 X 受体（PXR）激活相关，PXR 可抑制 NF-κB 的活性，削弱内毒素诱导的炎症介质释放，减少肠道上皮损伤；此外，利福昔明可以通过激活 PXR 抑制肿瘤坏死因子-α/肌球蛋白轻链激酶（TNF-α/MLCK）途径，加强上皮细胞紧密连接，从而改善肠道屏障功能[21]。FUJINAGA 等[22]研究发现，利福昔明对非酒精性脂肪肝也有抗纤维化作用，并且血管紧张素受体阻滞剂和利福昔明联合抗纤维化作用更强。另有研究证明，利福昔明对严重的酒精性肝炎也是安全的，可以明显减少临床并发症、急性失代偿及急慢性肝衰竭的发生，提高患者生存率[23]。这可能是未来临床预防酒精及非酒精性脂肪肝的新疗法，同时为其他肝病的治疗提供了新思路。

4 利福昔明对肝硬化难治性腹水的影响

难治性腹水患者预后不良，6 个月生存率约为 50%[24]。肝硬化患者肠道通透性增加、细菌位移导致循环中内毒素水平升高，肠源性内毒素诱导的炎性细胞因子增加可使肠系膜血管扩张，引起高动力循环，从而增加肝硬化腹水的难治性，而利福昔明可能通过影响肠道微生物群的结构和功能，降低炎症因子及内毒素水平，改善全身和肾脏血流动力学，从而对患者的短期生存率产生有益影响[16,25]。研究发现，利福昔明可降低患者肝静脉压力梯度（hepatic venous pressure gradient，HVPG），增加心输出量和全身血管阻力[26]，并降低白细胞介素（IL）-6 和 TNF-α 水平[27]。也有研究表明，利福昔明并未降低肝硬化腹水患者的 HVPG 或改善全身血流动力学，且不影响肾小球滤过率或血管活性激素水平[28]。目前，利福昔明治疗肝硬化难治性腹水的疗效尚不明确，需要更多高质量的随机对照试验来验证这些观点。

5 利福昔明对自发性腹膜炎的影响

肝硬化患者细菌易位增加导致细菌易感性增强，其发病受肠道通透性增加、免疫损伤和小肠细菌过度生长的影响[29]。细菌转移至肠腔外可形成自发性细菌性腹膜炎（spontaneous bacterial peritonitis，SBP），SBP 是肝硬化的一种重要感染性并发症，是晚期肝病的标志，与短期死亡率相关，因此，预防 SBP 对肝硬化患者预后有着重要影响。

最近一项 meta 分析显示，利福昔明在 SBP 的一级和二级预防中均有效，并且可能是唯一对二级预防有明显疗效的抗生素[30]。既往的欧洲肝脏病协会相关指南表明，诺氟沙星对 SBP 的一级和二级预防都有效[31]。而另外一项 mata 分析表示，与诺氟沙星、环丙沙星、甲氧苄啶-磺胺甲噁唑相比，给予利福昔明治疗似乎是预防肝硬化和腹水患者发生 SBP 的最佳方案[32]，支持利福昔明用于预防 SBP[33]。还有数据显示，利福昔明加乳果糖可明显降低 SBP 发生风险[34]，这可能与利福昔明抑制念珠菌及难治性梭状芽孢杆菌活性相关[35-36]；此外，利福昔明可以抑制艰难梭菌毒素诱导的细胞凋亡和紧密连接蛋白缺失，并且在降低死亡/移植风险方面优于其他抗生素[37]。总之，现有证据支持利福昔明用于 SBP 的预防，但还需要更多的随机对照试验进一步证实。

6 利福昔明对肝硬化伴食管胃底静脉曲张的影响

肝硬化并发门静脉高压可导致食管静脉曲张甚至出血，当门静脉压≥12 mmHg 时出血风险增加[38]，出血后即使通过内窥镜和药物治疗，患者死亡

率仍超过 15%[39]。研究发现，给予 LPS 腹腔预处理可使门静脉灌注压增加更明显[40]，并且 HSC 激活可能导致肝内血管过度收缩，从而增加血管阻力[41]，这可能是肝硬化患者细菌易位增加所致。而给予利福昔明治疗后，细菌易位相关标记物和促炎细胞因子水平均明显下降，提示利福昔明可通过抑制细菌易位而提高 HVPG 应答率，从而减少静脉曲张的发生[42]。另有研究也支持利福昔明与较低的静脉曲张破裂出血发生率相关，长期使用利福昔明可减少肝硬化患者门静脉高压相关并发症的发生，改善预后[43]。因此，对于静脉曲张及出血的患者，虽然内镜治疗是首选，但使用利福昔明可提高患者生存率，对指导临床用药有重要意义。

7 利福昔明对 HE 的影响

HE 主要表现为肝功能不全和门体分流引起广泛的神经精神异常，是一种可逆的脑功能障碍[44]，一旦出现，患者的生存率将降低，严重影响预后。根据美国、欧洲及日本的实践指南，给予乳果糖是显性 HE 的首选治疗方法[1,45]，可预防 HE 复发。而新的证据表明，添加利福昔明可提高二级预防效力，进一步降低 HE 复发和 HE 相关住院的风险[46]，并且对维持 HE 缓解也有显著作用，同时无患者因不良事件或并发症停药[47-49]。此外，利福昔明长期治疗包括 Child-Pugh C 在内的 HE 患者也是安全有效的[50]，还可以缩短住院患者的 HE 治疗时间，从而提高治疗的成本效益[51-53]。

利福昔明治疗 HE 的机制还未被完全阐述。目前被广泛认同的是其能抑制肠道产氨细菌。另外，在一项病例对照研究中，单因素分析表明利福昔明治疗 4 周后，内毒素活性水平降低与血清氨水平下降直接相关[54]。还有前瞻性研究发现，利福昔明可以通过调节肠道微生物群功能，影响 HE 相关代谢途径，如芳香氨基酸、支链氨基酸、内毒素合成及尿素循环，从而改善高氨血症和神经生理功能[55]。这提示利福昔明不仅具有抗菌作用，还可能作为肠道微生物群调节剂预防 HE 发生。此外，动物研究证明，利福昔明可防止外周免疫细胞渗入大脑，阻止神经炎症增强、神经传递改变，并改善认知和运动障碍[56]。并且，利福昔明对轻度 HE 患者的认知功能、健康相关生活质量及驾驶模拟器测试成绩有着积极影响[57-59]。最近一项 meta 分析也显示，利福昔明和乳果糖可明显逆转肝硬化患者的轻度 HE[60]。近年来研究还发现，利福昔明对经颈静脉肝内门体分流术(transjugular intrahepatic portosystemic shunt，TIPS)后并发症也有影响，可减少新发、进行性或复发性 HE 的发生，被考虑用于 TIPS 后 HE 的预防[61]，但其具体机制尚未被完全阐明，需要更多研究进一步证明。

8 利福昔明对肝癌的影响

肝硬化患者肠道通透性增加并伴有肠道屏障功能障碍，可促进微生物相关分子模式的转移，引发肝脏的先天免疫反应，从而诱导肝脏损伤并引起慢性炎症，最终导致肝癌[62]。而癌症患者由于恶性肿瘤的存在或治疗相关免疫抑制，具有较高的细菌感染风险[63]。有研究表明，LPS-TLR4 途径可介导肝祖细胞向肌成纤维细胞分化，提高 IL-6 和 TNF-α 表达水平，增加肝祖细胞数量，从而形成促肿瘤微环境，最终促进肝祖细胞的增殖和恶性转化[64]。并且，研究发现肠道微生物群可通过调节免疫反应影响肿瘤的功能[65]；另外，肠道微生物调节胆汁酸代谢也与抗肿瘤有关，分泌过多的短链脂肪酸引起胆汁淤积又可促进肝癌发生[66-67]。因此，利福昔明可能通过其屏障修复功能，以及调节肿瘤相关代谢途径等，对肝癌具有一定的预防及治疗作用。但在一项接受索拉非尼治疗晚期肝癌的研究中，包括利福昔明在内的抗生素治疗与较差的总体生存率相关，并且有缩短无进展生存期的趋势[68]。可见仍需要进一步的前瞻性研究验证包括利福昔明在内的抗生素是否对肝癌的防治有益。

9 利福昔明对肝硬化其他并发症的影响

进展期失代偿肝硬化会加速脂肪和蛋白质分解，最终导致脂肪组织和骨骼肌质量的丧失[69]，而肌肉减少症又将增加肝硬化相关并发症的发生风险，并对预后产生不利影响[70]。最近有研究发现，血清 TNF-α 水平升高与肌肉减少症发生相关。利福昔明可降低 TNF-α 表达，从而改善肝硬化动物模型的肌细胞减少症[71]。此外，有数据表明约 20% 的肝硬化患者会出现急性肾损伤，20% 的晚期肝硬化腹水或急性肝衰竭患者会出现肝肾综合征[72]。长期使用利福昔明，血肌酐和血尿素水平明显改善[25]。一些小样本研究和 meta 分析也证明，利福昔明对急性肾损伤和肝肾综合征有预防作用，并可以降低需要肾脏替代治疗的风险[73-74]。

10 小　结

利福昔明除了具有抗菌作用外，还可以通过改变肠道菌群组成与代谢等影响肠道微生物群，改善肠道通透性，降低内毒素活性，并稳定肠上皮细胞，减少细菌易位，从而减少内毒素血症的发生，减轻全身炎症反应，进而减少并发症的发生，最终影响肝硬化患者的代偿及失代偿。虽然利福昔明对肝癌的影响目前还未阐述清楚，但现有证据更多支持其有益作用。另外，利福昔明可以在不产生多药耐药细菌的情况下预防感染和其他肝硬化并发症，尽管其有益作用已被大量描述，还是需要更多强有力的证据论证其在 HE 以外的其他适应证中的应用。目前，利福昔明对包括肝硬化失代偿、急慢性肝衰竭及死亡等临床终点事件影响的研究较少，期待更多的高质量随机对照试验进一步研究利福昔明预防肝硬化和相关并发症及肝癌的潜在作用。

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