

原发性胆汁性肝硬化的治疗进展

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Progress in treatment of primary biliary cirrhosis

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Abstract

Primary biliary cirrhosis (PBC) is a chronic autoimmune cholestatic liver disease characterized by cholestasis, and it often eventually develops into cirrhosis, portal hypertension and liver failure. Asymptomatic patients typically are diagnosed by the elevation of alkaline phosphatase (ALP) and the presence of anti-mitochondrial antibody (AMA) titers of 1:40 or greater. Ursodeoxycholic acid (UDCA) is the only Food and Drug Administration approved treatment for PBC, but it is not universally effective. In patients with UDCA-refractory PBC, additional therapies should be considered, including budesonide, fibrates, obeticholic acid, immunosuppressants and liver transplantation.

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Key Words: Primary biliary cirrhosis; Treatment; Ursodeoxycholic acid; Budesonide; Fibrates; Obeti-

cholic acid; Immunosuppressants

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摘要

原发性胆汁性肝硬化(primary biliary cirrhosis, PBC)是一种以胆汁淤积为特点的慢性自身免疫性胆汁淤积性肝病, 最终发展为肝硬化, 门静脉高压及肝功能衰竭。临床无症状患者主要依靠肝功能碱性磷酸酶(alkaline phosphatase)异常及血清抗线粒体抗体(anti-mitochondrial antibody)阳性来诊断。熊去氧胆酸(ursodeoxycholic acid)是目前唯一被食品和药品管理局推荐用药, 但并不是所有的患者均有效, 因此布地奈德、贝特类、6- α 乙基鹅去氧胆酸(obeticholic acid)、免疫抑制剂、肝移植等应该被考虑用于PBC的治疗。

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关键词: 原发性胆汁性肝硬化; 治疗; 熊去氧胆酸; 布地奈德; 贝特类; 6- α 乙基鹅去氧胆酸; 免疫抑制剂

核心提示: 本文对原发性胆汁性肝硬化(primary biliary cirrhosis, PBC)的治疗进展做一综述, 熊去氧胆酸(ursodeoxycholic acid)是唯一被美国食品和药品管理局推荐用药, 但不是所有的患者均有效, 布地奈德、贝特类、6- α 乙基鹅去氧胆酸(obeticholic acid)、免疫抑制剂、肝移植等治疗应该被考虑用于PBC治疗。

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0 引言

原发性胆汁性肝硬化(primary biliary cirrhosis, PBC)是一种以胆汁淤积为特点的慢性自身免疫

■背景资料

原发性胆汁性肝硬化(primary biliary cirrhosis, PBC)是一种以胆汁淤积为特点的慢性自身免疫性胆汁淤积性肝病, 熊去氧胆酸(ursodeoxycholic acid, UDCA)是目前唯一被美国食品和药品管理局(Food and Drug Administration, FDA)推荐用药, 但并不是所有的患者均有效, 因此布地奈德、贝特类、6- α 乙基鹅去氧胆酸(obeticholic acid, OCA)、免疫抑制剂、肝移植等应该被考虑用于PBC的治疗。

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■研发前沿

OCA是人初级胆汁酸中鹅去氧胆酸的一种新型衍生物,通过激活法尼酯X受体(farnesoid-X-receptor),促进胆汁分泌和排泄,从而发挥抗纤维化以及逆转门脉高压的作用。该药已经在二期临床试验中取得较好的效果,目前进入三期临床试验。OCA可能为UDCA应答不良的患者带来福音。

性肝脏疾病,主要发生于中年女性,男女比例约为1:10^[1-3]。实验室检查以碱性磷酸酶(alkaline phosphatase, ALP)增高和血清抗线粒体抗体阳性为特点,临床以疲乏和瘙痒为主要症状,最终发展为肝硬化、门脉高压、肝功能衰竭^[4,5]。目前PBC胆管损伤机制尚不明确,考虑与基因和环境因素相关,环境因素作用于遗传易感者而发病^[6]。PBC的患病率可能因种族和地域差别而有所不同^[7,8],随着现代医学的发展和临床医师对PBC的认识加深,PBC的诊断率已显著提高^[7],越来越多的PBC患者可能处于无临床症状期而只存在肝功能异常而被诊断。对于PBC患者,早期识别、及时合理治疗是改善其预后的关键,关于PBC治疗的研究也不断深入,下面对PBC的治疗进展做一综述。

1 熊去氧胆酸的标准治疗

熊去氧胆酸(ursodeoxycholic acid, UDCA)是目前唯一被美国肝病研究学会(American Association for Study of Liver Diseases, AASLD)推荐并被美国食品和药品管理局(Food and Drug Administration, FDA)批准用于治疗PBC的药物^[5],也是目前最具有循证医学支持的非移植治疗PBC的药物,推荐剂量为13-15 mg/(kg·d)。UDCA为正常胆汁中的初级胆汁酸鹅去氧胆酸的7-β异构体,显著降低胆汁中胆固醇及胆固醇酯的量和胆固醇的饱和指数,UDCA能将胆汁酸转变为亲水性的毒力低的胆汁酸,具有扩张亲水性胆汁酸池,促进胆汁酸分泌,抑制胆汁酸或细胞因子诱导的细胞凋亡,并有免疫调节、抗炎、抗菌等作用^[9-11]。其作用机制还可能涉及趋化因子受体3(chemokine receptor 3, CXCR3)对PBC的介导作用^[12]。

大量研究^[13-16]表明,UDCA能显著改善肝脏生化学指标,延缓组织学发展,阻止肝纤维化及肝硬化的进展,提高生活质量,延长生存期。Boberg等^[17]对182例PBC患者UDCA治疗成本及效益的研究证实,UDCA不仅降低PBC死亡率及发病率,还可节省治疗费用。此外,良好的生化学应答与PBC非移植患者的生存率相关^[13,14,18]。Corpechot等^[19]也发现早期PBC患者UDCA治疗12 mo后胆红素开始恢复正常,天门冬氨酸氨基转移酶(aspartate transaminase, AST)和ALP<1.5×ULN(正常值上限),能实现较好的预后。虽然UDCA是PBC患者的最佳的选择,但并不是所有PBC患者对UDCA有良好的应答。大约1/3的患

者对UDCA治疗应答不良^[20],目前公认的PBC患者对UDCA应答可强力预测其远期疗效,以便及时确认是否应采取其他治疗方法^[21],多数以UDCA治疗1年的生化反应为预测标准,Zhang等^[22]也提出可通过治疗半年来判定疗效。以巴黎I标准为疗效判定依据^[14],即单用UDCA治疗1年后,ALP≥3 ULN,AST≥2 ULN,胆红素未降至正常者,判定为应答不良。Carbone等^[23]对2353例PBC患者的横断面研究发现,PBC患者对UDCA的治疗反应与性别和年龄密切相关,男性和年轻患者是UDCA应答不良的独立预测因子。对于UDCA治疗反应欠佳的患者,治疗上仍面临挑战,目前需要额外的治疗方案来解决这一难题^[24]。

2 法尼酯X受体激动剂

6-α乙基鹅去氧胆酸(obeticholic acid, OCA)是人初级胆汁酸中鹅去氧胆酸的一种新型衍生物,通过激活法尼酯X受体(farnesoid-X-receptor, FXR)^[25,26],促进胆汁分泌和排泄,从而发挥抗纤维化以及逆转门脉高压的作用^[27,28]。初步研究^[28,29]证实,OCA单独或联合UDCA治疗可显著改善PBC的生化指标,Fiorucci等^[30]报道165例UDCA应答不良的PBC患者加用OCA不同剂量组(10、25、50 mg),随访12 wk后结果显示,相比于单用UDCA组,治疗组ALP水平平均显著降低,然而50 mg大剂量OCA用于治疗PBC,严重的瘙痒致使患者不得不停药^[31-33]。一项关于140例未达到ALP≤1.67 ULN的PBC患者,加用OCA使24%的患者ALP得到改善^[33]。该药已经在二期临床试验中取得较好的效果,目前进入三期临床试验。OCA可能为UDCA应答不良的患者带来福音。

3 糖皮质激素

布地奈德是一种糖皮质激素受体和孕烷X受体(pregnane X receptor, PXR)激动剂,涉及胆汁酸的合成、代谢及转运^[28]。PBC患者肝脏组织的病理改变主要以非化脓性胆管炎或肉芽肿性胆管炎、汇管区炎症为特征^[34],因布地奈德具有高效抗炎,且主要通过肝脏首过消除,成为PBC患者的合理选择。大量数据表明,对于肝组织学存在界面炎的PBC患者,布地奈德联合UDCA能促进肝组织学及生化学改善^[35,36]。且对于早期PBC患者,布地奈德与UDCA短期联合治疗效果显著^[28]。Rabahi等^[36]对15例UDCA单独治疗欠佳的PBC患者采用UDCA、布地奈德及霉酚酸酯联

合治疗,发现三联疗法能明显改善生化学及组织学指标。布地奈德对PBC有一定的疗效,却不得不关注其严重的骨质疏松等不良反应^[37],且有报道^[38]称布地奈德可能与门静脉血栓形成相关。因此布地奈德用于治疗PBC我们需要在治疗效果及不良反应之间找到合理的平衡点。布地奈德适用于早期、肝组织学存在明显界面炎患者,推荐应用于PBC和自身免疫性肝炎(autoimmune hepatitis, AIH)重叠综合征。

4 贝特类药物

贝特类药物用于人类疾病已有很长的历史,包括苯扎贝特和非诺贝,是一种传统的降血脂药用于预防心血管疾病^[39]。目前贝特类药物用于治疗PBC只有部分机制被理解,贝特类药物是过氧化物酶体增殖物激活受体(peroxisome proliferator-activated receptor, PPAR) α 和PPAR γ 的双重激动剂,并可能通过影响PXR,抗胆汁淤积、抗炎、抗纤维化^[5,28,40]。在大鼠体内,贝特类药物也促进表达与炎症反应和胆汁酸代谢相关的多重耐药相关蛋白^[41]。许多研究^[40,42-44]表明贝特类药物能降低ALP、ALT和免疫球蛋白M(immunoglobulin M, IgM)水平。文献报道^[40,42,44,45]对UDCA应答不良的PBC患者,贝特类联合UDCA可以更显著地改善患者的肝功能生化指标。Lens等^[46]研究显示,苯扎贝特联合UDCA治疗能降低血清ALP等水平,而且明显缓解PBC的瘙痒症状。Honda等^[40]研究发现,贝特类还能通过下调胆汁酸的转运从而抑制胆汁酸的合成。最近的一项前瞻性多中心研究($n = 66$)表明,PBC患者苯扎贝特单一疗法能改善生化指标,对于UDCA单一疗法无效PBC患者,贝特类联合UDCA治疗能改善和维持正常的胆道酶^[47],这些积极的结果已在许多其他试点被成功复制^[42]。贝特类药物的耐受性良好,但部分患者会出现转氨酶的升高,且目前无贝特类药物治疗改善长期存活率相关报道^[21]。所以,贝特类药物用于治疗PBC,需要大量临床研究来加以明确。

5 免疫抑制剂

免疫抑制剂用于PBC患者发挥治疗作用的同时也抑制正常免疫功能,其中甲氨蝶呤和秋水仙碱用于治疗PBC有一个较长的历史。一些早期研究发现甲氨蝶呤和秋水仙碱有助于症状控制和生化指标改善^[29,48,49]。2004年的一项基于8项临床研究的Meta分析表明,与安慰剂相比,秋

水仙碱并不能显著改善患者的死亡率和肝移植率^[50]。也有报道秋水仙碱联合UDCA超过10年的随访能改善肝组织坏死性炎症得分,但很少或几乎不影响患者的组织学分期和患者的生存率^[49]。而最近发表的一项涉及370例患者的Meta分析显示,与安慰剂相比,甲氨蝶呤尽管能缓解患者的瘙痒症状,但并不能对患者的生化指标产生影响,也不能提高患者的生存率^[51]。而其他的免疫抑制剂如环孢素、硫唑嘌呤、苯丁酸氮芥和D-青霉胺,鉴于其潜在的巨大不良反应与不确切的疗效,目前尚不推荐常规用于PBC的治疗^[26,52,53]。

6 肝移植

PBC的早期诊断及药物治疗能明显改善预后,提高生活质量。Kuiper等^[54]研究结果表明,因UDCA的应用,目前荷兰PBC患者进行肝移植的比例已从11.5%下降至4.5%,但肝移植仍然是治疗终末期PBC患者的唯一有效方法。根据Mayo风险评分和终末期肝病模型(model for end-stage liver disease, MELD)评分,选择合适的时机进行肝移植^[55]。PBC接受同种异体肝移植后疾病复发高达30%-35%^[56],他克莫司被推荐用于管理移植后复发,移植后UDCA治疗PBC复发没有共识,据报道移植后1年和5年的存活率分别为92%和85%^[26]。

7 其他治疗方法

目前还提出了关于抗逆转录病毒药物、骨髓间充质干细胞和分子疗法(如anti-CD20、CD80、CXCL10、抗白介素-12)用于治疗PBC^[6,22,29,57-63],但均属于小样本量研究,其长期有效性及安全性尚需扩大规模进行临床研究。

8 讨论

PBC是一种慢性自身免疫性肝脏疾病,UDCA 13-15 mg/(kg·d)能改善生化学指标,延缓PBC组织学进展,是目前PBC患者首选的治疗药物。患者一旦确诊为PBC,长期UDCA治疗及合理的疾病管理应该被推荐,对于UDCA应答不良的患者,根据患者的年龄、组织学生化指标合理加用其他治疗药物,UDCA联合免疫抑制剂是PBC-AIH重叠综合征的标准化治疗方案,新的治疗方法,如OCA、贝特类为PBC患者带来了新的希望。而终末期PBC患者,肝移植为唯一有效治疗方法。

■ 相关报道

Fiorucci等报道165例UDCA应答不良的PBC患者加用OCA不同剂量组(10、25、50 mg),随访12 wk后结果显示,相比于单用UDCA组,治疗组碱性磷酸酶(alkaline phosphatase, ALP)水平均显著降低,然而50 mg大剂量用于治疗PBC,严重的瘙痒致使患者不得不停药。

■创新盘点

贝特类药物用于人类疾病已有很长的历史,能抗胆汁淤积、抗炎、抗纤维化。许多研究表明贝特类药物能降低ALP和免疫球蛋白M。但目前无贝特类药物治疗改善长期存活率相关报道。所以,贝特类药物用于治疗PBC,需要大量临床研究来加以明确。

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■应用要点

患者一旦确诊为PBC, 长期UDCA治疗及合理的疾病管理应该被推荐, 对于UDCA应答不良的患者, 根据患者的年龄、组织学及化学指标合理加用其他治疗药物。而终末期PBC患者, 肝移植为唯一有效治疗方法。

■同行评价

本文综述了PBC的研究进展,无症状患者主要依靠肝功ALP异常及血清抗线粒体抗体阳性诊断。UDCA是唯一被FDA推荐用药,但不是均有效。布地奈德、贝特类、OCA、免疫抑制剂、肝移植应该被考虑用于PBC治疗。文献较新,具有一定的参考价值。

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