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慢性眼部移植物抗宿主病治疗的研究进展

柯婉仪，周敏，蔡乐琪 综述 万鹏霞 审校

(中山大学附属第一医院眼科，广州 510080)

[摘 要] 眼部移植物抗宿主病发生在超过一半的慢性移植物抗宿主病患者中，涉及眼表持续的炎症以及纤维化改变，最常见的表现为干燥性角膜结膜炎。严重的眼部移植物抗宿主病不但影响患者的工作和生活质量，同时也增加了其他眼部并发症的风险。慢性眼部移植物抗宿主病的治疗主要包括局部应用人工泪液、血清类制剂、抗炎药物等药物治疗，佩戴隐形眼镜、睑板腺按摩等物理治疗、封闭泪点、重建眼表等手术治疗。随着对眼部移植物抗宿主病发病机制的深入研究，许多新的治疗药物和治疗手段涌现临床。总结目前慢性眼部移植物抗宿主病在药物治疗、物理治疗、手术治疗方面的最新研究进展，将有助于为慢性眼部移植物抗宿主病的治疗带来更多选择和更新的研究思路。

[关键词] 眼部移植物抗宿主病；干眼；眼表；治疗；环孢素

Research progress in the treatment of chronic ocular graft-versus-host disease

KE Wanyi, ZHOU Min, CAI Leqi, WAN Pengxia

(Department of Ophthalmology, First Affiliated Hospital of Sun Yat-Sen University, Guangzhou 510080, China)

Abstract More than half of the patients developed chronic graft-versus-host disease after accepting allogeneic hematopoietic stem cell transplantation suffer from ocular graft-versus-host disease. Ocular graft-versus-host disease involves persistent inflammation and fibrosis of the ocular surface and keratoconjunctivitis sicca is the most common symptom. Severe ocular graft-versus-host disease not only affects patients' life quality, but also increases the risk of other ocular complications. The treatment of chronic ocular graft-versus-host disease mainly includes drug treatment, such as local application of artificial tears, serum eye drops and anti-inflammatory drugs; physical treatment, such as wearing contact lenses and meibomian gland massage; surgical treatment, such as punctal occlusion and reconstructing ocular surface. With the in-depth study of the pathogenesis of ocular graft-versus-host disease, many new therapeutic drugs and methods have emerged. Summarizing the latest research progress in

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通信作者 (Corresponding author)：万鹏霞，Email: wanpengx@mail.sysu.edu.cn
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drug, physical and surgical therapy of chronic ocular graft-versus-host disease will give us insights into treatment options and hot spot of research.

Keywords ocular graft-versus-host disease; dry eye; ocular surface; treatment; cyclosporin

慢性移植物抗宿主病(chronic graft versus host disease，cGVHD)是同种异体造血干细胞移植(allogeneic hematopoietic stem cell transplantation，allo-HSCT)之后最常见的长期并发症，涉及组织炎症和纤维化改变，通常会导致永久性器官功能障碍[1-3]。cGVHD的主要靶器官是眼睛、肝、皮肤、肺、胃肠道、口腔[1]，其中眼部受累的发生率大于50%[4-5]，通常在异基因造血干细胞移植后6个月至3年内出现[5-7]。眼部GVHD可影响眼睛的所有部位，其中眼表最常受累[6]。T细胞介导的炎症反应以及随后发生的免疫级联反应会导致眼表的炎症细胞浸润和腺体纤维化，引起泪液成分的改变、泪膜不稳定，进而导致眼表损害[1,4]。干眼或干燥性角膜结膜炎(keratoconjunctivitis sicca，KCS)是慢性眼部GVHD最常见的表现[8-9]，其症状包括畏光、视物模糊、眼干、眼痒和眼部异物感等[8-9]。在严重患者中，由于角膜或眼内并发症，最终可能导致永久性视力丧失，严重影响患者的生活质量[7,10]。

慢性眼部GVHD的治疗旨在缓解干眼症状，持续控制炎症并防止组织的不可逆损伤[11]，需要多种治疗方式协同实现。传统的药物治疗主要包括使用人工泪液、血清类制剂、抗炎药物等；物理治疗包括加强睑板腺护理以改善睑板腺功能、佩戴接触镜缓解泪液蒸发等缓解措施；手术治疗包括封闭泪点以延长泪液在眼表的停留时间、利用移植物重建眼表等。近年来，随着对眼部移植物抗宿主病发病机制的深入研究，许多新的治疗药物和治疗靶点不断涌现。本文主要论述了近年来慢性眼部GVHD在药物治疗、物理治疗、手术治疗方面的研究进展。

1 药物治疗

1.1 人工泪液

频繁使用不含防腐剂和磷酸盐的人工泪液进行局部润滑是慢性眼部GVHD的一线治疗[12-13]。对于轻度干眼，可选择黏稠度较低的人工泪液，对于中重度干眼，可选择黏稠度较高的人工泪液或眼用凝胶、眼膏以延长药物在眼表的停留时间[14-15]。

1.2 促泪液分泌剂

眼表上皮细胞产生和分泌黏蛋白，糖基化的黏蛋白有助于维持泪膜，保持眼表湿润以及防止病原体黏附和入侵[16]。研究[17]发现：在眼部GVHD小鼠模型中，黏蛋白水平明显降低，糖基化程度显著减少。瑞巴派特和地夸磷索通过促进黏蛋白分泌从而稳定泪膜，改善干燥引起的角膜损伤，此外，地夸磷索还能够促进泪液的分泌[18-20]。两者已成功显现出对慢性GVHD相关干眼的治疗效果[17,21-22]。

1.3 血清类制剂

近几十年来，血源性滴眼液已被广泛应用于包括眼部GVHD在内的各种眼表疾病的治疗中。人类血清成分与泪液相似，包含多种生长因子、细胞因子、维生素A和免疫球蛋白等，其中一些成分的浓度高于其在天然泪液中的浓度，因此，用血清制成的滴眼液除了能够润滑眼表，还可以促进眼表上皮细胞的增殖、迁移和分化，从而维持角膜和结膜的完整性[23-27]。在制备自体血清滴眼液(autologous serum eye drops，ASED)时，患者的外周血清可能含有高浓度的促炎症细胞因子，局部应用可能增加眼表炎性反应。此外，全身或血管情况较差的患者可能无法获得血液样品[28-30]。同种异体外周血血清或脐带血血清滴眼液可作为ASED的替代方案，其中脐带血血清的生长因子含量高于外周血血清，是一种强大的生物补充剂来源[31-32]。然而，使用同种异体血清具有传播血源性疾病和发生过敏反应的风险，还必须考虑使用同种异体血清的伦理和法律问题[30]。近年来，各种血小板制剂如富生长因子血浆和血小板裂解物在眼表疾病中的使用有所增加。相比AS，血小板制剂中含有更高水平的生长因子和更低水平的促炎介质，因此，其在加速眼表损伤的愈合和减轻眼表炎症方面比AS更有效[33-38]。已有前瞻性研究证明了富生长因子血浆滴眼液、血小

板裂解物滴眼液治疗慢性眼部GVHD的长期安全性和有效性[33,36-37]。

1.4 抗炎药物

基于炎症在眼部GVHD发病过程中的关键作用，多种抗炎药物已被用于治疗慢性眼部GVHD患者。尽管局部使用皮质类固醇能够减轻眼表炎症并改善干眼的体征和症状[39]，但长期使用皮质类固醇所带来的诸如眼内压升高和白内障、青光眼和感染性角膜炎等并发症限制了其在临床上的使用[13]。此外，有研究[40]表明：与非GVHD相关的干眼患者相比，GVHD相关干眼患者对局部类固醇治疗反应较差。

目前已研发出许多能够克服皮质类固醇毒副作用的免疫抑制剂作为慢性眼部GVHD的抗炎药物。环孢素A(cyclosporin A，CsA)通过抑制钙调神经磷酸酶介导的T淋巴细胞活化并下调炎性细胞因子的表达，减轻结膜和泪腺的炎性浸润，从而增加结膜杯状细胞密度，改善泪液分泌，并促进眼表上皮细胞的更新[41-42]。对于常规润滑剂和局部类固醇治疗无效的慢性眼部GVHD患者，局部应用0.05%CsA可改善患者的干眼症状、增加基础泪液的分泌以及促进角膜损伤修复[43]。另一种钙调神经磷酸酶抑制剂——他克莫司的作用机制与CsA相似，具有免疫抑制效力更强、患者耐受性更好等优点，可能适用于对CsA局部或全身不耐受的眼部GVHD患者[44-46]。细胞间黏附分子-1(intercellular adhesion molecule-1，ICAM-1)与淋巴细胞功能相关抗原-1(lymphocyte function associated antigen-1，LFA-1)的相互作用与同种异体反应性淋巴细胞向GVHD靶器官的转运、T细胞的激活以及随后的免疫细胞介导的组织损伤有关[47]。立他司特是一种小分子整合素拮抗剂，通过阻断LFA-1与ICAM-1的结合抑制T淋巴细胞介导的炎症[48-50]。在一项对18名慢性眼部GVHD患者的回顾性队列研究[49]中，立他司特滴眼液治疗导致8名患者的症状有所改善，其余10名患者保持症状稳定。立他司特在眼部GVHD中的疗效仍有待观察。

近年来针对其他靶点的抗炎药物也在研发中。Janus激酶(Janus kinase，JAK)与脾酪氨酸激酶(spleen tyrosine kinase，SYK)在T细胞活化和炎症中发挥关键作用，JAK和SYK抑制剂抑制同种异体反应性和自身反应性T细胞用于治疗全身性GVHD[51-52]。一项II期临床试验[53]证明了新型JAK/SYK联合抑制剂R348滴眼液可以有效治疗严重慢性眼部GVHD患者的角膜上皮损伤。结膜下注射间充质干细胞(mesenchymal stromal cells，MSCs)除了有效减轻小鼠角膜中的T淋巴细胞浸润、减少炎症细胞因子的表达外，还能够抑制眼部GVHD诱导的角膜鳞状化生，提示MSCs的局部应用可作为慢性眼部GVHD患者的一种新的治疗选择[54]。

随着中性粒细胞在眼部GVHD中的病理生理作用的发现，针对减少眼表中性粒细胞及其细胞外产物从而治疗眼部GVHD的新型生物疗法也在开发中。中性粒细胞胞外杀菌网络(neutrophil extracellular traps，NETs)促进眼部GVHD的病理变化，包括角膜上皮病变、结膜瘢痕形成、睑板腺损伤和眼表炎症，An等[55-56]通过动物实验和早期临床试验初步证明肝素滴眼液、重组脱氧核糖核酸酶滴眼液可通过降解NETs来减轻眼部GVHD。Kwon等[57]研究证明人类免疫球蛋白滴眼液可通过抑制促炎性细胞因子释放和NETs的产生减轻慢性眼部GVHD相关的干眼症状。

1.5 抗纤维化药物

除免疫细胞介导的慢性炎症外，眼表纤维化是cGVHD的另一个突出的病理特征[4-5]，近年来抗纤维化的新型药物也正在研发中。导管周围区域是cGVHD患者泪腺纤维化的主要部位，成纤维细胞在此活化并合成热休克蛋白47(heat shock protein 47，HSP47)和I型、III型胶原蛋白，抑制HSP47的表达后体内和体外的胶原蛋白合成减少[58]。Ohigashi等[58]研究发现：使用携带HSP47siRNA的维生素A偶联脂质体滴眼液治疗泪腺纤维化的cGVHD小鼠，能够使小鼠泪液分泌增加，泪腺纤维化程度改善，证明HSP47有望成为慢性眼部GVHD治疗的新靶点。重链透明质酸-正五聚蛋白3(heavy chain-hyaluronan/pentraxin 3，HC-HA/PTX3)是从人羊膜纯化的复合物，已知具有抗炎和抑制疤痕形成的作用[59]。结膜下注射HC-HA/PTX3可以抑制慢性GVHD小鼠模型的泪腺和结膜中炎性细胞的浸润和纤维化，提示HC-HA/PTX3可能作为治疗慢性眼部GVHD的一种更有效的选择[59]。肠道微生物群与全身免疫系统之间存在关联，因此使用抗生素治疗cGVHD的研究也在进行中[60-61]。口服庆大霉素能显著减轻cGVHD小鼠的

眼部表现和GVHD靶向器官中的炎症细胞浸润和纤维化[62]。未来还需前瞻性实验确认这些药物对慢性眼部GVHD患者的作用。

1.6 其他药物

研究[63-64]显示：存在睑板腺炎性反应的患者可局部使用1.5%阿奇霉素滴眼液、口服营养补充剂Omega-3脂肪酸或者四环素类抗生素，减轻炎性反应，改善腺体分泌功能，增加泪膜稳定性，从而改善干眼的体征和症状。

2 物理治疗

对于存在睑板腺功能障碍的慢性眼部GVHD患者，积极进行睑缘清洁、定期热敷、睑板腺按摩等物理治疗有助于睑脂排泄，改善腺体功能[3]。目前市场上出现各种加热装置，如热脉动治疗、强脉冲光治疗可持续改善睑板腺功能并缓解干眼症状[65-69]。

对于患有持续性上皮缺损或角膜变薄的患者，佩戴软性角膜绷带镜有助于稳定泪膜，促进角膜愈合，有效改善患者的眼部症状[70-71]。软性角膜绷带镜获取方便且价格便宜，可作为眼部GVHD患者的首选镜片，但是对于严重干眼的患者治疗效果不佳[70,72]。大直径的巩膜镜与角膜之间形成泪液库，可以延长泪液的润滑时间，保护角膜免受眼睑的机械摩擦，以及有助于形成均匀的屈光面，从而实现最佳的光学负荷，优化视力[72-74]。但巩膜镜的生产成本较高、配制时间较长，且只在少数地区可以获取[70]。此外，角膜水肿或内皮功能障碍是巩膜镜治疗的并发症和禁忌证，使用巩膜镜片期间应监测角膜内皮功能[74-76]。

3 手术治疗

当药物以及其他治疗方法无法缓解病情时需采用手术进行治疗。泪点封闭是眼部GVHD相关干眼的辅助治疗之一，通过抑制泪液排出使眼表保持湿润，改善干眼症状和体征[77-79]。由于患者泪点上皮下纤维化，与非GVHD相关的干眼患者相比，GVHD相关干眼患者的泪点塞保留率更低[77]。对于反复发生泪点再通或泪点塞脱落的患者，可使用热烧灼法进行永久封闭泪点[80-82]。

严重的干眼患者可行临时或长期睑缘缝合术以减少眼表暴露[83]。发生持续角膜上皮缺损或角膜溃疡、角膜穿孔范围较小的患者可进行羊膜移植，羊膜作为角膜上皮细胞的支架，含有多种抗炎和营养因子，可抑制炎症并促进角膜上皮快速愈合，防止进一步的角膜穿孔[84-85]。此外，羊膜来源的细胞具有强烈的免疫抑制特性，能够预防严重眼部GVHD的复发[85]。对于角膜穿孔较大(>3 mm)或难治性角膜溃疡的眼部GVHD患者建议行角膜移植术[86]。若患眼持续存在炎症或角膜新生血管，穿透性角膜移植术后发生植片融解、二次穿孔、移植免疫排斥反应等严重并发症的风险增加，总体预后较差[85,87-88]。板层角膜移植术显著降低移植排斥的风险[89]。在羊膜上扩增的自体或同种异体角膜缘干细胞可用于角膜缘干细胞缺乏症的眼部GVHD患者重建角膜[90-91]。同种异体角膜缘干细胞移植同样具有较高的移植排斥风险[87]。近年来有研究[90,92-93]报道了移植来自同一造血干细胞供体的角膜缘干细胞或结膜干细胞能够成功恢复眼表，并且能建立长期的免疫耐受，无需进行全身免疫抑制治疗。同时也有研究[94]发现人类口腔黏膜干细胞表达与角膜上皮细胞相关的标志物，具有向角膜上皮细胞分化的潜力，可能成为角膜置换的材料。

4 结语

慢性眼部GVHD相关干眼是allo-HSCT术后并发症中不可忽视的一部分，有必要对其进行干预，以减轻患者眼部不适，改善患者生活质量，避免严重的并发症。尽管慢性眼部GVHD的治疗依旧具有挑战性，但是近年来在其药物治疗、物理治疗、手术治疗方面均发展出许多新的治疗选择，以期在提高疗效的同时减少不良反应的发生。未来应进行更多的研究，以确认这些方法的长期安全性和有效性，为慢性眼部GVHD干眼患者提供更有效的治疗选择。

开放获取声明

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