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【述评】

干眼炎症诊疗规范:2023 欧洲专家共识解读[△]

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由于存在局部潜在不良事件,如眼压升高,白内障和机会性感染,外用皮质类固醇只能在有限的时间内使用^[13,18],此时可以考虑用氟米龙、氯替泼诺和氢化可的松,因为它们增加眼压和诱发白内障形成的可能性较低^[13,18]。大量的研究和 Meta 分析表明,环孢素是一种有效的干眼治疗药物,具有可耐受的安全性,与皮质类固醇相比,它可以安全地延长给药时间^[13,14]。

3 环孢素在干眼治疗中的应用

3.1 环孢素治疗的时机

关于环孢素治疗的时机,欧洲专家们一致认为,使用环孢素滴眼液治疗干眼炎症的时机应取决于角膜和结膜染色的严重程度、免疫相关系统疾病的存在与否、患者对皮质类固醇治疗的反应速度快慢以及在接受标准护理治疗时炎症的受控制程度。然而,专家们也认为,对于有严重干眼危险因素的患者,应考虑尽早外用环孢素进行治疗,以控制炎症。在干眼中,角膜和结膜染色、结膜充血和泪液生成减少是眼部炎症发生的重要标志,但如果存在其他危险因素,即使没有严重的角膜染色出现,局部也应采用环孢素滴眼液展开治疗。

与局部皮质类固醇治疗一样,当泪液替代品、眼睑卫生和环境控制无效时,局部应用环孢素也适合于干眼的二线治疗^[13,18-22]。对其他炎症性疾病的研究结果也表明,在病程中早期施用环孢素可解决炎症反应问题,如早期使用环孢素治疗溃疡性结肠炎可以改善预后并降低结肠炎发病率^[23]。环孢素已被证明在以炎症为主要病理特征的疾病(如银屑病、特应性皮炎和白塞综合征)中具有起效快速的特点,治疗几周后便能观察到炎症得到显著改善^[24-26]。

3.2 环孢素治疗评估的时间

专家们一致认为,对环孢素的治疗效果应在患者接受治疗1个月后进行评估,并每3个月进行一次评估,以确认疗效。施用环孢素后第一个月内患者的初始反应明显,该阶段的疗效可以通过干眼的一些体征和症状改善情况表现出来,但患者干眼程度改善通常出现在治疗6~8周后,在治疗3~6个月干眼程度可得到维持或进一步改善^[19-20,27]。此外,在环孢素给药前15~20 min,给予人工泪液可显著改善环孢素滴注前的烧灼、刺痛和刺激症状^[28]。

3.3 环孢素和皮质类固醇的联合治疗

对于干眼,在开始局部环孢素治疗的同时或治疗前不久使用皮质类固醇短期治疗(桥接)可获得更好的疗效^[18,29-31],这能使患者的干眼症状和体征得到迅速改善,同时对外用环孢素的耐受性也有所提高。局部滴用环孢素应在皮质类固醇治疗的同时或在治疗一周内开始,皮质类固醇剂量应根据炎症症状和体征的变化逐渐减少。

众所周知,限制局部皮质类固醇使用的主要原

因是长期使用这些药物会引起一些不良反应,如眼压升高和白内障形成,这些副作用在短期使用时也可能产生^[13-14,18,31-33]。因此,监测使用皮质类固醇治疗的患者是十分必要的。在皮质类固醇和局部环孢素联合治疗时,患者需接受眼科检查,在治疗1~2周后密切监测患者眼压^[18,33],并每2~4周完成一次OSDI评估^[29-31]。效力较低/渗透性较低的皮质类固醇与效力较高的制剂相比,可能具有较低的眼压和白内障风险^[13,18,31],可以考虑作为替代治疗方案,以减少不良事件发生的风险。

3.4 环孢素治疗的减量和停用

对于干眼这种慢性疾病应采取长期治疗的策略,最终的目的在于恢复患者眼表的稳态^[11-12,14,32]。研究表明,长期局部应用环孢素对干眼患者可提供持续的益处,在长期的治疗中患者体征和症状甚至能完全缓解,并可以减少剂量或完全停止治疗^[13,18,34-35]。尽管某些患者有复发的风险,但 Labetoulle 等^[34]对患者进行24个月随访分析后发现,大多数患者(61%)在使用环孢素改善干眼后无复发。因此,专家们建议,如果患者对环孢素治疗保持良好的耐受性和有效性,则可以无限期地继续治疗;如果已达到充分和持续的改善,则可适度减量或停止治疗。

两项长期研究^[34-35]证实了患者对环孢素的长期耐受性,未发现具体的长期安全性问题。此外,在临床试验中,患者出现全身性治疗相关不良事件的发生率也非常低,并且无全身性严重不良反应的报道^[34-35]。尽管如此,专家小组仍建议在耐受性差或缺乏疗效的情况下,应停止使用环孢素。

干眼是青光眼和白内障患者的常见并发症,针对这些疾病的眼科手术可能会加重干眼症状。同时,眼表疾病可能会对手术效果产生负面影响,因此,在手术前优化眼表对于确保更好的手术效果非常重要^[32,36-37]。专家小组建议,如果干眼患者正在接受手术,则应继续接受环孢素治疗。

3.5 环孢素的疗效、安全性和耐受性

3.5.1 环孢素的疗效

环孢素的疗效应在治疗1~3个月后进行评估。环孢素疗效评估的主要指标是体征和症状的改善情况,包括视力模糊的减少、眼表面染色的减少和泪膜破裂时间的改善。在治疗的第一个月内,通过干眼体征和症状的显著改善证明患者对环孢素的初步反应明显^[38],在治疗的第4周,接受局部环孢素治疗的患者的角膜荧光素染色严重程度可显著改善,这种改善一直可保持到治疗的第12个月^[39]。

3.5.2 环孢素的安全性和耐受性

在临床试验和实践中,外用环孢素引发的大多数治疗突发不良事件都发生在眼部,其中最常见的是滴注部位的疼痛和刺激。大多数不良事件的严重程度为轻度至中度,很少有严重不良事件的报告。

这种良好的耐受性意味着只有一小部分患者因不良事件需要停止外用环孢素治疗。对于那些在局部使用环孢素后出现滴注部位疼痛和刺激的患者,专家建议可以采取额外的措施来缓解不适,如在施用局部环孢素前大约 20 min 给予不含防腐剂的人工泪液,在施用局部环孢素后约 20 min 给予无防腐剂的凝胶,对于缓解疼痛和刺激是有帮助的。在外用环孢素治疗开始前或与环孢素联合使用 4 周,使用非穿透性、无防腐剂的类固醇可以提高局部耐受性^[18]。除此之外,眼科医师还应该向患者说明外用环孢素阳离子乳剂的产品信息,建议滴眼液必须在常温、避光的环境中储存^[40]。

4 患者教育

专家组表示在使用局部环孢素之前和期间对患者进行教育对优化治疗的依从性至关重要。环孢素的疗效主要取决于患者的依从性和治疗的持久性,不遵守治疗方案会影响患者生活质量、视力和工作效率,有时由于持续存在的症状甚至会导致患者对治疗效果不满。研究表明,患者教育可以克服局部环孢素的依从性问题,特别是在需要长期治疗干眼时尤显重要^[41]。不坚持治疗或停止使用环孢素的患者所引发的常见后果,包括治疗不耐受和起效延迟^[41-42],因此告知患者环孢素的效果不是立即显现的非常重要。虽然干眼本质是慢性疾病,但多数患者可能会在症状得到初步缓解后认为他们的病情得到了很好的控制从而暂停治疗^[43-44]。此外,应告知患者在治疗开始时可能需要使用皮质类固醇作为过渡性治疗,他们需要继续使用滴眼液以减少眼部不适的感觉。在开始局部环孢素治疗之前,应告知患者潜在的不良症状,例如滴注时可能出现疼痛和烧灼感甚至刺痛,眼科医师应鼓励患者坚持治疗,提示他们这些不良症状通常是短暂的,并会随着眼表情况的改善而减轻^[45]。

5 结束语

干眼是一种慢性眼表炎症性疾病,如果治疗不当,可能导致患者角膜的严重损害,甚至影响视力。尽管类固醇一直是大多数炎症性疾病(包括干眼)的主要治疗药物,但非糖皮质激素免疫调节剂,特别是环孢素,作为不使用类固醇的局部治疗方法,在干眼的治疗中已经取得突出的地位。然而,如何更好地使用环孢素仍然是一个具有临床意义的问题。

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Specification for diagnosis and treatment of inflammation in dry eye: interpretation of the European Expert Consensus 2023

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[Abstract] Dry eye (DE) is a multifactorial chronic ocular surface disease. Patients often report pain, with inflammation being one of the primary causes of ocular surface pain in DE. Anti-inflammation is the most critical tool in the treatment of DE. The latest inflammatory diagnosis and treatment specifications for DE are detailed in the *Diagnosis, Management and Treatment of Inflammation in Dry Eye; Recommendations of the European Expert Working Group on the Management of Inflammation in Dry Eye*. This article provides a comprehensive interpretation of the consensus, aiming to improve the diagnosis and treatment levels of DE among medical practitioners and better serve ophthalmic patients.

[Key words] dry eye; inflammation management; diagnosis and treatment; guideline interpretation