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2020年赴湖北黄石抗击新冠疫情,担任当地小汤山医院-黄石中医院(市传染病院)业务副院长,带领江苏援黄队员及所在医院当地医护人员共同抗疫,顺利完成任务,获得“江苏省抗击新冠肺炎疫情先进个人”称号。

## 大环内酯类抗生素治疗哮喘的研究进展

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**摘要:**哮喘是一种慢性气道炎症性疾病,吸入性糖皮质激素是其主要治疗药物。然而,少部分患者无法得到有效控制,对于此类患者亟需新的治疗方法。近年来,除了生物制剂的研究外,对于大环内酯类抗生素在哮喘治疗中的潜力也备受关注。本文就大环内酯类抗生素治疗哮喘的疗效、可能机制和不良反应进行系统综述。

**关键词:**肺疾病;支气管哮喘;大环内酯类抗生素;急性加重;治疗方法

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## Research progress of the treatment of asthma with macrolide antibiotics

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**Abstract:** Asthma is a chronic inflammatory disease of the airways, and inhaled corticosteroids are the main treatment. However, a small number of patients cannot be effectively controlled, and new treatment methods are urgently needed for such patients. In recent years, in addition to the research on biological agents, there has been considerable interest in

the therapeutic potential of macrolide antibiotics in asthma. This article provides a systematic review of the efficacy, possible mechanisms, and adverse reactions of macrolide antibiotics in the treatment of asthma.

**Key words:** Pulmonary disease; Bronchial asthma; Macrolide antibiotics; Acute exacerbation; Treatment method

支气管哮喘是一种常见的慢性呼吸系统疾病,据统计,全球约3亿人患哮喘,其中儿童和青少年患病率约为10%,成人患病率约为6%~7%<sup>[1-2]</sup>。部分患者尽管使用了中高剂量吸入性糖皮质激素(inhaled corticosteroids, ICS)联合长效 $\beta$ 受体激动剂(long acting  $\beta$ -receptor agonist, LABA)或维持性口服皮质类固醇激素,但哮喘症状仍不能得到控制<sup>[3]</sup>,此类难治性哮喘严重影响患者生活质量及生命安全,加重其经济负担<sup>[4]</sup>。大环内酯类抗生素是链霉菌属产生的一组天然产物<sup>[5]</sup>,除了经典抗菌作用外<sup>[6]</sup>,还具有免疫调节特性<sup>[7]</sup>。近期已有应用大环内酯类药物治疗多种慢性气道疾病的探讨<sup>[8]</sup>,然而大环内酯类抗生素在哮喘中的疗效尚无一致结论。本文就大环内酯类抗生素治疗哮喘的机制、临床疗效及不良反应进行综述。

## 1 大环内酯类抗生素治疗哮喘的作用机制

### 1.1 抗感染作用

病原体感染是导致支气管哮喘急性发作的主要诱因,据报道,病毒感染约占儿童急性发作诱因的80%,在成人中其比例也超过50%,且大多与鼻病毒感染有关<sup>[9-10]</sup>。哮喘患者鼻病毒感染期间,支气管上皮表达干扰素较正常人群显著减少,这可能与鼻病毒诱导的哮喘恶化程度重及病毒载量高相关<sup>[11]</sup>。阿奇霉素可抑制鼻病毒复制并增强其诱导的干扰素表达,发挥抗病毒作用<sup>[12]</sup>。此外,阿奇霉素还可有效减少哮喘患者(特别是中性粒细胞型哮喘患者)诱导痰中流感嗜血杆菌计数,降低气道炎症水平<sup>[13]</sup>。

### 1.2 抗炎作用

现已明确,多种炎症因子参与哮喘的发生发展<sup>[14]</sup>。大环内酯类抗生素通过调节细胞信号转导,抑制炎症细胞对相关细胞因子和炎症介质的产生来发挥抗炎作用。研究证实,大环内酯类抗生素可减少多种促炎因子的产生,如白细胞介素(interleukin, IL)-1 $\beta$ 、IL-6、IL-8、IL-17以及肿瘤坏死因子- $\alpha$ (tumor necrosis factor- $\alpha$ , TNF- $\alpha$ )等<sup>[13]</sup>。据报道,大环内酯类抗生素可通过抑制Toll样受体-4介导的信号传导,下调核因子- $\kappa$ B的信号转导与转录激活因子1的表达,降低TNF- $\alpha$ 表达水平,并阻止中

性粒细胞募集到肺中<sup>[15-16]</sup>。另有研究发现,大环内酯类药物还可降低嗜酸性粒细胞特异性细胞因子及趋化因子表达,促进嗜酸性粒细胞凋亡,抑制骨髓来源的嗜酸性粒细胞的增殖<sup>[17]</sup>。此外,大环内酯类药物还可减弱由肺成纤维细胞趋化的嗜酸性粒细胞募集<sup>[18]</sup>,降低IL-33诱导的嗜酸性粒细胞炎症<sup>[19]</sup>。

### 1.3 改善气道重塑

研究表明,长期口服阿奇霉素可显著下调低氧诱导因子-1 $\alpha$ 和血管内皮生长因子表达,抑制成纤维细胞和血管内皮细胞的增殖,从而减少纤维组织沉积和血管生成,改善气道重塑<sup>[20-21]</sup>。但也有研究指出,接受阿奇霉素治疗的哮喘患者,气道壁厚度没有明显变化<sup>[22]</sup>。

### 1.4 减少气道黏液分泌

气道黏液分泌过多是哮喘的重要特征。大环内酯类药物可通过抑制促炎细胞因子如TNF- $\alpha$ 、IL-13表达及黏蛋白5AC分泌来抑制杯状细胞增殖及气道黏液分泌<sup>[23-25]</sup>。另有研究表明,大环内酯类药物可能通过影响气道氯离子通道,部分激活毒蕈碱受体,抑制黏膜下腺细胞的钙离子内流,从而减少气道中黏液分泌<sup>[26-27]</sup>。

### 1.5 调节肠道菌群作用

近期研究发现,阿奇霉素可通过改变肠道菌群影响哮喘患者的气道炎症<sup>[28]</sup>。在接受阿奇霉素治疗后,哮喘小鼠肠道中梭菌目显著升高,梭菌可能通过产生短链脂肪酸限制嗜酸性粒细胞的迁移和存活来减轻过敏性气道炎症<sup>[29-30]</sup>。另有研究表明,阿奇霉素处理的哮喘小鼠肠道中醋酸盐水平升高,可降低气道高反应性及肺泡灌洗液中2型炎症细胞因子水平,减少气道黏液的产生<sup>[28]</sup>。

## 2 大环内酯类治疗哮喘的临床应用

### 2.1 研究进展

此前对于大环内酯类药物治疗慢性气道炎症方面的研究主要集中在慢性阻塞性肺疾病(chronic obstructive pulmonary disease, COPD)方面,慢性炎症和感染是COPD及其急性加重的重要机制,大环内酯类抗生素可通过其抗感染及抗炎作用,有效减少COPD急性加重,改善患者的生活质量<sup>[31]</sup>。对于急性加重的COPD患者,亦能有效控制病情,降低

其死亡率<sup>[32]</sup>。一项评估阿奇霉素治疗 COPD 安全性的研究证实,在长达 1 年余的治疗中,COPD 住院率持续降低且不良事件发生率很低<sup>[33]</sup>。

由于哮喘的复杂发病机制及其异质性,在使用大环内酯类药物治疗哮喘的研究中,其疗效仍存在争议。一篇纳入了 23 项研究的荟萃分析表明,大环内酯类药物不能改变哮喘患者临床结局,如急性加重、症状控制、生活质量等<sup>[34]</sup>,随后开展的一项多中心随机对照试验也未观察到阿奇霉素治疗哮喘的症状评分及急性加重率的改善,但其结果可能受疗程过短的影响<sup>[35]</sup>。一项纳入 2 万余例成人和儿童哮喘患者的初级医疗保健系统中开展的观察性研究表明,加用大环内酯类抗生素后并不能改变急诊就诊或住院人数<sup>[36]</sup>。

但近年来,随着研究的进一步深入及观察疗程的延长,越来越多证据表明大环内酯可用于治疗哮喘。Gibson 等<sup>[37]</sup>开展了一项纳入 420 例患者的多中心、双盲、安慰剂对照研究,患者随机接受阿奇霉素/安慰剂治疗(3 次/周,500 mg/次,持续 48 周),结果表明阿奇霉素治疗组经历 1.07 次/(人·年)加重,相较于安慰剂组的 1.86 次/(人·年),加重次数明显减少;治疗结束时,阿奇霉素组患者哮喘生活质量调查问卷评分比安慰剂组高出 0.63,差异有统计学意义;患者的哮喘控制问卷评分表明,鼻部症状、咳嗽咳痰症状均得到改善。几项荟萃研究均表明,大环内酯类药物治疗哮喘在减少口服类固醇激素、短效  $\beta$  受体激动剂及其他抗生素使用中具有积极作用<sup>[38-40]</sup>。此外,也在一定程度上减轻哮喘急性发作时的经济负担<sup>[41]</sup>。GINA 也建议,对于使用高剂量 ICS-LABA 下哮喘症状仍持续的成人患者,经专科医生评估后可考虑附加阿奇霉素(建议 3 次/周,治疗至少 6 个月)。但在添加阿奇霉素之前,应检查痰液是否存在非典型分枝杆菌,心电图是否为长 QT 间期,并充分考虑增加抗菌药物耐药性的风险<sup>[42]</sup>。

虽然尚无指南推荐儿童哮喘患者使用阿奇霉素,但近年来越来越多的研究表明,大环内酯类药物治疗可显著改善儿童肺功能,减少短效  $\beta$  受体激动剂使用,减少鼻拭子中卡他莫拉菌计数,降低喘息风险,且儿童发生不良事件的风险较低。各项研究中,阿奇霉素的用量及疗程存在差异,但总体来说,疗程大于 3 周的治疗效果更佳<sup>[43]</sup>。近期一项针对哮喘控制不佳患儿的随机对照试验发现,使用阿奇霉素患儿(10 mg/kg,3 次/周,持续 3 个月)的儿童哮喘控制测试评分优于对照组,其急诊就诊率和急性加重次数均显著减少,但两组间呼出气一氧化氮、肺功

能参数、咽拭子阳性率、诱导痰中性粒细胞百分比变化及不良反应发生率均无差异<sup>[44]</sup>。目前,阿奇霉素仍是最常用且推荐的大环内酯类抗生素,也有研究提示克拉霉素能改善哮喘患儿的肺功能并减轻嗜酸性粒细胞炎症,减少急性加重<sup>[45-46]</sup>。

## 2.2 影响大环内酯类药物疗效的因素

支气管哮喘是一种异质性疾病,复杂的基因和环境相互作用导致了哮喘的不同表型和内型<sup>[47]</sup>。大环内酯类药物对不同哮喘表型的疗效可能存在差异,因此,进一步的亚组分析可以一定程度上解释临床试验中模棱两可的结果。Brusselle 等<sup>[48]</sup>在一项多中心双盲随机对照试验中发现,阿奇霉素治疗对哮喘患者的急性加重及症状控制无显著改善,但可显著减少非嗜酸性粒细胞哮喘(non-eosinophilic asthma, NEA)(血嗜酸性粒细胞  $\leq 200/\mu\text{L}$ )患者的急性发作,并改善哮喘评分。也有研究表明,阿奇霉素对流感嗜血杆菌及炎症标志物(如 IL-6、IL-1 $\beta$ 、TNF- $\alpha$ )的抑制作用主要体现在 NEA 患者中<sup>[13,49]</sup>。除阿奇霉素外,其他大环内酯类抗生素(如克拉霉素)也被证实可显著降低难治性 NEA 患者气道中 IL-8 浓度和中性粒细胞数量,降低中性粒细胞弹性蛋白酶和基质金属蛋白酶浓度<sup>[50]</sup>,降低气道炎症,改善生活质量评分。

气道炎症因子水平也会影响阿奇霉素的疗效,研究者通过测定哮喘患儿急性发作期鼻黏膜上皮黏液中炎症介质水平发现,较低的 TNF- $\alpha$  和 IL-10 水平以及较高的趋化因子配体 22 水平常表现出对阿奇霉素治疗更好的反应性<sup>[51]</sup>。

2021 年,Thorsen 等<sup>[52]</sup>开展了一项针对儿童哮喘患者的研究,发现在哮喘急性发作期间,患儿气道中细菌  $\alpha$  多样性及某些特定细菌聚落单位(operational taxonomic unit, OTU)与发作持续时间增加相关,而阿奇霉素可改善这种情况,特别是对于某些特定 OTU(如韦荣氏球菌属、明串珠菌属、弧菌属),其丰度越高,阿奇霉素治疗作用越强。此外,有研究表明,哮喘患者诱导痰中流感嗜血杆菌丰度越高,阿奇霉素治疗效果越好,哮喘急性发作越少<sup>[53]</sup>。综上,气道菌群也可能影响大环内酯类药物的疗效。

## 3 长期使用大环内酯类药物治疗的潜在危害

### 3.1 不良反应

总体来说,哮喘患者对阿奇霉素治疗耐受性良好,与安慰剂组相比,不良事件的总体发生率无显著

差异,不良反应主要表现于胃肠道,如恶心呕吐、腹痛腹泻,但在不同类型大环内酯类药物或不同给药途径之间没有差异<sup>[54]</sup>。英国胸科协会关于大环内酯类药物在成人呼吸系统疾病中的应用指南建议,如果在较高剂量(500 mg,3次/周)的阿奇霉素治疗下出现胃肠道不良反应,可以考虑将剂量减至250 mg,3次/周<sup>[55]</sup>。

相关研究指出,大环内酯类药物可延长QTc间期(按心率校正的QT间期),增加心律失常及心血管死亡风险<sup>[56-57]</sup>。因而对于QTc>450 ms的男性及QTc>470 ms的女性,指南不推荐使用大环内酯类药物<sup>[58]</sup>。在根据指南建议使用阿奇霉素治疗呼吸系统疾病的研究中,并没有发现该不良反应的增加<sup>[59-60]</sup>,在儿童及老年群体中,药物安全性也得到证实<sup>[61-62]</sup>。但也有研究发现,阿奇霉素会增加依赖血液透析的肾功能衰竭患者的心源性猝死风险<sup>[63]</sup>。

### 3.2 细菌耐药性增加

尽管2017年的一项随机对照实验没有报告阿奇霉素治疗哮喘会导致细菌耐药性增加<sup>[37]</sup>,但是Taylor等<sup>[64]</sup>研究表明,阿奇霉素治疗未控制哮喘患者时,在检出的89个抗生素耐药基因中,5个大环内酯类耐药基因显著增加。此外,有研究指出,阿奇霉素耐药的全球患病率正在增加<sup>[65]</sup>,故而在选择大环内酯类药物治疗哮喘时,需全面评估适应证及检测耐药性。

### 3.3 呼吸道微生物组改变

研究发现,长期接受阿奇霉素治疗,可降低患者呼吸道中卡他莫拉菌和流感嗜血杆菌丰度,接受治疗一年后的呼吸道微生物以流感、副流感病毒、铜绿假单胞菌及嗜麦芽窄食单胞菌为主。不仅如此,阿奇霉素治疗还改变了微生物代谢产物及炎症因子表达,对其治疗效果及抗生素耐药性亦可能产生影响<sup>[66-67]</sup>。而在短期(4周)阿奇霉素治疗前后,未发现呼吸道微生物的改变<sup>[68]</sup>。

### 3.4 哮喘风险增加

尽管大多数研究表明大环内酯类药物治疗哮喘有益,但将其应用于儿童哮喘患者时需要更慎重。2020年,Lin等<sup>[69]</sup>对过敏性鼻炎儿童的病例分析发现,过去5年使用抗生素(特别是青霉素和大环内酯类药物)与儿童12岁前发生哮喘的风险增加相关,且呈剂量-反应关系。

综上,大环内酯类抗生素作为一种广谱抗菌药物,可以通过多种途径发挥抗炎作用,抑制气道黏液分泌及气道重塑,在控制哮喘症状、减少急性加重次数中发挥积极作用。阿奇霉素是应用最广泛的大环

内酯类抗生素之一,其在哮喘中的治疗作用已在越来越多的临床研究中得到证实。总体来说,大环内酯类药物耐受性良好,但也有发生消化道不良反应及耐药性增加的风险。还需进一步研究来明确大环内酯类抗生素的最佳使用方式,包括剂量、疗程和给药方法等。与其他药物的联合治疗以及个体化治疗等领域也有待进一步探索,为哮喘患者提供更为有效和个性化的治疗策略。

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