· Review in English ·

Cysteinyl leukotrienes antagonists as a treatment for children with asthma

Robert KLEINMAN, Marco MURA, Ming-Yao LIU

Thoracic Surgery Research Laboratories, Toronto General Hospital Research Institute, University Health Network, Departments of Surgery, Medicine and Physiology, Faculty of Medicine, University of Toronto, Toronto M5G 2C4, Canada

Abstract: Children have the highest prevalence of asthma, an obstructive lung disease characterized by bronchoconstriction, persistent airway inflammation and airway remodeling. Inhaled corticosteroids and β2-agonists add-on therapies are used to treat these children but these medications are not always effective, and inappropriately high doses of corticosteroid may lead to serious side effects such as osteoporosis, growth retardation, and glaucoma. Oral anti-leukotrienes are new treatments for children suffering from asthma that work by antagonizing leukotrienes and inhibiting their synthesis. Leukotrienes are lipids synthesized from arachidonic acids in the 5-lipoxygenase pathway by mast cells, eosinophils, and alveolar macrophages in the lungs. Leukotrienes are involved in the asthmatic response by binding to the CysLT1 receptor on the airway smooth muscles, causing bronchoconstriction. Recent studies have shown that the cysteinyl-leukotrienes may mediate subepithelial collagen deposition and smooth muscle hypertrophy and hyperplasia, causing irreversible airway remodeling and airway obstruction. Experimental studies and preliminary clinical reports on pediatric patients have shown that the leukotriene antagonist montelukast may prevent airway remodeling and reduce asthmatic symptoms when used as an add-on treatment to reduce the intake of corticosteroids and β2-agonists. However, the efficacy of anti-leukotrienes drugs still needs to be confirmed by randomized, double-blind and multicenter clinical trials.

[**Chin J Contemp Pediatr, 2005, 7(5):398 – 403**]

Key words: Asthma; Cysteinyl leukotrienes; Montelukast; Airway remodeling

半胱氨酰白三烯拮抗剂治疗儿童哮喘

Robert KLEINMAN, Marco MURA, Ming-Yao LIU 多伦多大学医学院外科及生理学系,加拿大 多伦多 M5G 2C4

[**摘 要**] 哮喘是一种梗阻性肺疾病,以支气管收缩、持续性气道炎症和气道重塑为特征。临床上常用吸入皮质激素和 β2 受体拮抗剂辅佐治疗儿童哮喘,但这些药物疗法的治疗效果不是很理想,而且不适当的大剂量皮质激素会导致骨质疏松,生长迟缓和青光眼等严重副作用。口服抗白三烯剂是一种治疗儿童哮喘的新方法。白三烯是由花生四烯酸通过 5-脂肪氧化酶途径由肥大细胞、嗜酸粒细胞和肺泡巨噬细胞合成的脂质。它通过与气道平滑肌上的 $CysLT_1$ 受体结合参与哮喘的炎症反应而引起支气管收缩。最近的研究表明,半胱氨酰白三烯可以介导上皮下胶原沉着和平滑肌肥大增生,从而导致不可逆的气道重塑和气道阻塞。实验研究和初步的临床研究显示,白三烯拮抗剂孟鲁司特辅助治疗儿童哮喘,可以减少皮质激素和 β2 拮抗剂的用量,预防气道重塑、减轻哮喘症状。然而,抗白三烯药物的疗效还需通过随机、双盲和多中心的临床研究得到进一步证实。

[**中国当代儿科杂志,2005, 7(5):398 – 403**]

[**关 键 词**] 哮喘;半胱氨酰白三烯;孟鲁司特;气道重塑

[**中图分类号**] R562.2⁺5 [**文献标识码**] A [**文章编号**] 1008 – 8830(2005)05 – 0398 – 06

In the recent Workshop Report published by the Global Initiative for Asthma (GINA), it is stated that the prevalence of asthma symptoms in children varies from 0 to 30 percent in different populations, with Australia, New Zealand and United Kingdom having the highest prevalences[1]. Asthma is a complex obstruc-

[Received] May 25, 2005; [Revised] July 20, 2005
[Foundation Item] Supported by Canadian Institutes of Health Research Grants MOP-13270 and MOP-42546.
[Biography] Robert KLEINMAN (1983 –), Male, Medical student.
[Correspondence Author] Ming-Yao LIU, Departments of Surgery, Medicine and Physiology, Faculty of Medicine, University of Toronto, Toronto M5G 2C4, Canada (Email: mingyao.liu@utoronto.ca).

tive airway disease characterized by bronchoconstriction, airway inflammation, and airway remodeling. These responses, associated with allergies, exercise, and cold temperatures, can be life threatening if not treated promptly and properly[1]. Symptoms of asthma include cough (usually worse at night), wheezing, dyspnea, activity limitation, and nighttime waking due to shortness of breath[1].

Based on the 2004 GINA guidelines[1], the classification of asthma in children over 5 years old is based primarily on the frequency and severity of symptoms: intermittent (less than once a week); mild persistent (more than once a week but less than once a day); moderate persistent (daily symptoms that affect activity and sleep); severe persistent (daily symptoms that limit physical activity).

While no daily medication is recommended for children with intermittent asthma, children with more severe symptoms are recommended to be placed on a daily controller therapy, primarily based on inhaled corticosteroids plus long-acting β2-agonists (for moderate and severe persistent asthma), with increasing dosages with increasing symptom severity[1]. However, high doses of corticosteroid may lead to serious side effects such as osteoporosis, growth retardation, and glaucoma [1,2].

Anti-leukotrienes represent the newest type of asthma medications. However, large-scale, controlled clinical trials are still needed to confirm their efficacy in asthma. Therefore, anti-leukotrienes are currently only considered as add-on therapeutic agents. Over 50 chemical messengers have been found to mediate asthma[3] and one of these mediators is the Slow Reacting Substance of Anaphylaxis (SRS-A)[4], which causes sustained bronchoconstriction. In 1979, it was discovered that SRS-A is comprised of LTC_4, LTD_4, and LTE_4 cysteinyl-leukotrienes[4]. Twenty years later, anti-leukotriene medications, which may potentially antagonize leukotrienes and inhibit their synthesis, became clinically available, though for now their usefulness is only supported by animal studies and clinical studies of limited extent.

This article will examine the biochemistry of cysteinyl leukotrienes, their role in asthma-induced bronchoconstriction and airway remodeling, and the potential usefulness of their inhibitors as treatments for pediatric asthma.

Biosynthesis of cysteinyl leukotrienes

Cysteinyl-leukotrienes are synthesized from arachidonic acid, a membrane phospholipid derived from lineolic acid, in the 5-lipoxygenase pathway (Figure 1). This pathway is initiated in mast cells, eosinophils, and alveolar macrophages with C_4 synthase, when they are induced by stimuli such as IgE binding to FcεRI receptors, hyperventilation, aspirin (in aspirin intolerant individuals), hypoxia, hyperoxia, and exposure to platelet activating factor[5]. The result is that arachidonic acid is cleaved from the cell membrane by cytosolic phospholipase A_2. The arachidonic acid is sequentially metabolized to leukotriene LTA_4, LTB_4, LTC_4, LTD_4 and LTE_4 by the lipoxygenase enzyme cascade[6]. A variety of anti-leukotriene medications (*e. g.* zileuton) work by inhibiting the synthesis of cysteinyl leukotrienes through the 5-lipoxygenase pathway[7].

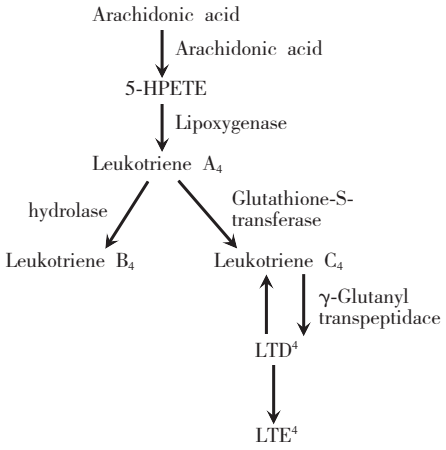

Figure 1 The formation of leukotrienes through the 5-lipoxygenase pathway. Adapted from Reference 5

Cysteinyl leukotrienes mediate bronchoconstriction

Initial research concerning cysteinyl-leukotrienes investigated their role in mediating prolonged contractions of airway smooth muscle. Asthmatic and non-asthmatic patients inhaling aerosolized leukotrienes, LTC_4 and LTD_4, show a significant decrease in their forced expiratory flow (FEV_1), caused by a bronchoconstriction that lasts from 20 to 30 minutes[8]. A concentration of the cysteinyl-leukotrienes 3 000 times less than that of histamine is sufficient to initiate this response, suggesting that the cysteinyl-leukotrienes are very potent mediators of bronchoconstriction[9]. Assays of LTE_4 in excreted urine, used as indicators of cysteinyl leukotriene production, have shown elevated levels in adult asthmatics[10].

The cysteinyl-leukotriene receptor $CysLT_1$ on

airway smooth muscle is currently recognized to mediate the effects of the bronchoconstriction[11]. CysLT1 is a 7-transmembrane G-protein coupled receptor that binds preferentially to $LTD_4 > LTC_4 > LTE_4$[11]. Nevertheless, the expression of the CysLT1 receptor in asthmatic and non-asthmatic patients is not significantly different, which suggests that asthma is not related to an altered expression of $CysLT_1$[12].

$CysLT_2$ is another cysteinyl-leukotriene receptor expressed on pulmonary vascular endothelium [13], although it does not seem to play roles in bronchoconstriction.

Montelukast as a treatment for pediatric asthmatics

Chewable montelukast is the leukotriene antagonist that is most commonly prescribed for pediatric patients.

Safety of montelukast

Montelukast has been found to be well tolerated in children aged 2-14 years. During 4 clinical trials, with one lasting as long as 1.8 years, adverse side effects compared against the placebo treatment were found not to be significantly different [14-17]. A decrease in the response to repeated administrations of montelukast was not evident in an 80-week trial period with patients aged 6 to 14 years [18].

The response to accidental overdose of medication is another important issue to consider for pediatric patients. No symptoms were observed in two cases of unintentional overdose ingestion of 80 mg montelukast in a 3-year-old asthmatic child and 135 mg montelukast in a 5-year-old asthmatic child [19]. Doses <4.5 mg/kg in children are considered minimally toxic [19-20].

Churg-Strauss syndrome (CSS) is a potentially fatal disorder that is characterized by blood vessel inflammation and eosinophil proliferation. The diagnosis of CSS is based on at least four of the following six features: moderate to severe asthma; peripheral blood eosinophilia ($>10\%$); mononeuropathy or polyneuropathy; pulmonary infiltrates, paranasal sinus abnormality; extravascular eosinophils [21]. Several cases of CSS have been reported in association with therapy with leukotriene antagonists, including montelukast [21]. Each of these patients had a history of multiple asthma exacerbations that often required systemic corticosteroids for control [22]. In the majority of these cases the appearance of CSS was associated with a reduction in the corticosteroid systemic dose [22]. The occurrence of CSS in asthmatic patients receiving leukotriene antagonists appears to be related to the unmasking of an underlying vasculitic syndrome that is initially clinically recognized as moderate to severe asthma and treated with corticosteroids. Therefore, montelukast does not appear to directly cause the syndrome in these patients. So far, no pediatric or adults patients in any of the clinical trials performed showed symptoms of blood vessel inflammation and eosinophil proliferation that were related to CSS [14-17]. Nevertheless, this potential risk warrants further investigation and great attention during treatment with montelukast; thus physicians must be especially vigilant for it in patients whose corticosteroids are tapered [22].

Efficacy of pediatric montelukast use

Recent studies that have examined the effects of montelukast on children aged 2-14 years with intermittent and persistent asthma and have shown it to be effective in reducing symptoms [5,15,16,17]. Symptoms considered included coughing, wheezing, dyspnea, activity limitation, and nighttime waking due to shortness of breath. In a trial on pediatric patients aged 2-5 years, all of these symptoms were reduced but not completely relieved [15]. In an 8-week clinical trial, performed in 2000, it was shown that the FEV_1 was significantly improved in asthmatic children aged 6-14 years taking montelukast, in comparison with those taking a placebo [17].

However, in the authors' opinion, comparing the results of montelukast to placebo treatments does not indicate that it can be used as an alternative to corticosteroids because in a metanalysis of 14 trials, corticosteroids were still found to be more effective at providing rescue bronchodilation and relieving exacerbations [23].

Montelukast as an add-on therapy

As an add-on therapy, montelukast would be clinically beneficial if it could reduce the use of corticosteroids in order to decrease the uncommon but potentially harmful side effects [24].

A 12-week trial on children with persistent asthma, who were dependent on glucocorticoids, showed that the addition of 5 mg of montelukast to regular treatments of 200 μg of budesonide produced a significant increase in FEV_1 ($P=0.01$, compared to placebo) and a decrease in β_2-agonist use ($P=0.01$, compared to placebo) [25]. The most relevant observation was a 23% reduction in exacerbation days, leading the authors to recommend that oral cysteinyl leukotriene-receptor antagonists should be combined with inhaled glucocorticoid therapy if the inhaled corticosteroids

alone do not fully control the symptoms of the persistent asthma [25]. Unfortunately, there is little evidence to suggest that montelukast therapy produces steroid-sparing effects. A clinical trial testing this effect on asthmatic children treated with low to moderate doses of inhaled corticosteroids (ICS) showed that during the ICS tapering period, the percentage reduction in ICS dose was not significantly different between montelukast-treated and placebo-treated subjects ($P=0.10$) [26].

It has, however, been shown that montelukast is a more effective add-on treatment than the commonly used cromolyn sulfate, a mast cell inhibitor, because it reduced the puffs per day of albuterol, a β-agonist, more than cromolyn sulfate. As an add-on treatment, montelukast is therefore preferred to inhaled medication [27]. A pediatric study demonstrated that parent and patient satisfaction for montelukast was 82% compared to 17% for cromolyn sulfate [27]. This is likely correlated to the significantly higher adherence to the montelukast treatment in the trial [19].

Cysteinyl leukotrienes and airway remodeling

Several recent animal reports suggest that cysteinyl leukotrienes may be involved in long-term airway remodeling that irreversibly decreases lung function, although large clinical studies are still needed to confirm this hypothesis.

Airway remodeling is predominantly the result of subepithelial collagen deposition and muscle hypertrophy and hyperplasia [28]. This remodeling contributes to the thickening of the airway walls and enhances the degree of lumina narrowing during smooth muscle contraction [28]. It is debated whether hyperplasia of mucus glands and goblet cells is associated with asthma because there is no correlation between asthma severity and this hyperplasia [29]. While it is also still unclear whether airway remodeling is caused by airway inflammation or is a natural outcome of the disease, it certainly results in irreversible airway obstruction [30]. In a study conducted over 15 years, there was a significant difference between the decrease of FEV_1 in adults without asthma (22 mL/year) compared to the decrease in FEV_1 of adults with self-reported asthma (38 mL/year), which the Authors suggested is caused by airway remodeling [31]. At present, there is not any similar long-term study on pediatric patients.

Cysteinyl leukotrienes may be involved in the airway structural remodeling in patients with persistent asthma. *In vitro* studies showed that smooth muscle tissue taken from human lungs and incubated in medium exhibited an increased migratory response to platelet-derived growth factor, when incubated with LTE_4 for 30 minutes [32]. Montelukast inhibited this response and this suggests that the response is mediated by binding of the LTE_4 to the $CysLT_1$ receptor [32].

Montelukast to reduce airway remodeling

Recent murine experiments, which are considered to be appropriate models for human asthma, have shown evidence supporting the role of cysteinyl leukotrienes in airway remodeling and that this remodeling can be relieved by antagonizing the $CysLT_1$ receptor. In one study, female BALB-C mice were treated for 6-8 weeks with ovalbumin (OVA), a chemical agent used to induce allergic asthma in mice [33]. Mice treated with montelukast had significantly reduced airway remodeling and obstruction caused by airway hyperplasia, fibrosis, and mucus proliferation [33]. In another study, BP2 mice challenged with OVA were found to respond within 15 minutes with increased cysteinyl leukotriene levels in the bronchoalveolar lavage [34]. Airway remodeling was blocked by epidermal growth factor receptor (EGFR) inhibitors, anti-leukotriene antagonists, and 5-lipoxygenase pathway inhibitors [34]. This also suggests interplay between EGFR and leukotrienes in airway remodeling [34].

Although the evidence from these experiments suggest that montelukast can play a role in preventing airway remodeling, it should be noted that clinical testing on humans confirming the results achieved in animals have not yet been carried out. A preliminary report from a 4-year follow-up study of 7 chronic asthmatic pediatric patients taking montelukast and fluticasone propionate has so far examined the effects of leukotriene antagonists on airway remodeling. High resolution computed tomography scan showed a decrease in low-density areas in the children's lungs, which the authors referred to be suggestive of a reduction in subepithelial fibrosis due to montelukast use [35]. Since this is a pilot study, more reports are necessary to confirm this finding.

Conclusions

Although the cysteinyl leukotrienes were initially thought to be potent mediators of the asthmatic response, pediatric clinical studies have shown that they are not effective substitutes for corticosteroids, downgrading them to add-on therapies to reduce the dosages of corticosteroids. On the other hand, recent experimental evidence on animals suggest that cysteinyl leukotrienes may be involved in mediating airway

remodeling and that their inhibition may significantly inhibit this pathologic process. While the relationship between airway remodeling and lung function is still unclear, the abnormal airway growth of children with persistent asthma has been shown to promote the persistence and severity of the asthma in later years [28]. Preventing this remodeling with anti-leukotriene medication implies the possibility to improve lung function in these subjects, possibly even before they become symptomatic [36]. However, the role of leukotrienes in remodeling is still only a hypothesis that requires controlled clinical studies to confirm the results that have been achieved in animal testing. These proposed clinical studies should also test the safety of the anti-leukotriene medication on its long-term application.

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(Edited by Le ZHONG)

·病例报告·

小儿脾脓肿 1 例

张喜凤,石红蕾,王道昉

(聊城市第二人民医院,山东 临清 252601)

[中图分类号] R657.6+1 [文献标识码] E

患儿,男,1 岁,因发热 7 d 于 2004 年 8 月 12 日入院。患儿入院前 7 d 发热,体温波动于 38℃ ~ 39℃,热型不规则,当地予以先锋霉素肌肉注射治疗,效果不佳,入院前 3 d 体温达 39 ~ 41 ℃,伴寒颤,精神差、纳差,不伴腹痛。平素经常感冒,无结核病史及密切接触史。体查:T 37.8℃,P 120 次/min,R 30 次/min,体重 12 kg,急性病容,神清,精神差,面黄,耳后淋巴结肿大,前囟近闭,咽部充血,颈软,心肺正常,腹膨隆,肝于右锁骨中线肋缘下 3 cm 可触及,脾肋下 7 cm,质韧,全腹无明显压痛及反跳痛,移动性浊音阴性。门诊实验室检查:血常规:WBC 18.8×10^9/L,RBC 3.35×10^{12}/L,N 0.441, L 0.559 ,HB 94 g/L ,PLT 131×10^9/L。胸片示右肺纹理增重、模糊,有小点片状阴影。入院诊断:支气管肺炎,败血症。予以青霉素、卓立佳、病毒唑抗炎治疗,并进一步完善各项辅助检查,血沉 56 mm/h ,CRP >6 mg/L(正常 <6 mg/L),肝、肾功、心肌酶无异常,乙肝全套阴性,血培养无需氧菌生长,PPD-IgM(-),肥达反应、抗核抗体、抗链球菌溶血素 O 及类风湿因子均阴性,骨穿示感染骨髓象,肝胆脾 B 超示肝脾大,肝肋下 3 cm,脾肋下 7 cm,脾内探及 1.0 ~ 2.0 cm 多发低回声区,边界较模糊,内回声欠均质,脾 CT 示多发低密度改变,有 1.0 cm × 1.0 cm 到 1.5 cm × 2.0 cm 大小,结合临床考虑脾脓肿(多发),经会诊转小儿外科,行剖腹探查见脾脓肿破裂、膈下脓肿,脓液培养有大肠埃希菌生长,行脓液引流及继续加强抗炎治疗 10 d,痊愈出院。

脾脓肿临床极少见,因脾脏是一个微生物高效滤过器,含有大量吞噬细胞,可以清除外来细菌及异物,具有抵抗感染的免疫力,少数细菌感染不易形成脓肿,多发生在有慢性病、体质衰弱、有免疫缺陷的患儿,常由细菌或巨细胞病毒感染引起,其中以链球菌、葡萄球菌、大肠杆菌感染最多见,多为血源性感染,邻近的化脓病灶可直接侵入脾实质,还可因脾实质内出血灶、坏死灶继发感染形成脓肿,早期很少与周围组织粘连,晚期位于脾脏表面者,与周围血管粘连,张力较大,时常穿入其他器官或破溃入腹腔。临床上主要表现为寒颤、高热、左上腹疼痛,腹肌紧张,脾区压痛、反跳痛,约 1/3 患儿脾大,白细胞增多,常伴贫血,X 线检查可见左膈肌升高,有些病例有胸腔积液,膈下有软组织包块,超声提示脾大和脾内液体积聚,对确诊有重要价值,治疗主要为针对病原抗炎及局部脓肿处理相结合,效果不佳者可行脾切除术,预后大多良好,重症可并发败血症死亡。此患儿年龄小,病情进展快,短期内脓肿破裂,临床未见报道。

(本文编辑:吉耕中)

[收稿日期]2005 - 06 - 24;[修回日期]2005 - 08 - 01
[作者简介]张喜凤(1972 -),女,大学,主治医师。主攻方向:小儿呼吸消化系统疾病。