

Antileukotrienes in rhinosinusitis and nasal polyposis

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Nasal polyposis is a chronic inflammatory disease of the nasal and paranasal sinus mucosa that, despite different hypotheses of its cause, remains poorly understood. The management of nasal polyposis has been the topic of countless frequent controversial debates for many decades. International guidelines generally suggest that first-line treatment should be based on a medical approach with mainly nasal and oral corticosteroids. Surgical procedures are often viewed as adjunctive to medical therapy. Given that antileukotrienes are currently indicated in the treatment of asthma and allergic rhinitis and there exists an increased leukotriene production in nasal polyps, antileukotrienes, especially montelukast, may represent a potential effective therapy for chronic rhinosinusitis, including nasal polyps.

KEYWORDS: antileukotrienes • chronic rhinosinusitis • leukotrienes • nasal polyps

Nasal polyps (NPs) appear as grape-like structures in the upper nasal cavity, originating from the ostiomeatal complex. They consist of loose connective tissue, edema, inflammatory cells and some glands and capillaries, and they are covered with varying types of epithelium, mostly respiratory pseudostratified epithelium with ciliated cells and goblet cells. Eosinophils are the most common inflammatory cells in NPs, but neutrophils, mast cells, plasma cells, lymphocytes and monocytes are also present, as well as fibroblasts. IL-5 is the predominant cytokine in NPs, reflecting activation and prolonged survival of eosinophils [1,2].

Nasal polyps are often associated with asthma and other respiratory diseases, such as cystic fibrosis, primary ciliary dyskinesia and aspirin sensitivity [3], as well as, more recently, with idiopathic bronchiectasis [4]. Several mechanisms have been proposed for the development of NPs, but the common final pathway seems to be an integrated process involving the mucosal epithelium, the matrix and inflammatory cells and mediators. This cycle may be initiated by infectious and non-infectious mechanisms. In a postulated cell-mediated immune reaction in the pathogenesis of NP formation, steroids would act on the immune response by inhibiting cytokine production from a number of cells, such as

T cells, eosinophils or epithelial cells. In addition to T-cell activation, a number of studies have demonstrated prostanoid and leukotriene (LT) release, as well as other arachidonic acid (AA) metabolites in NPs, from patients with chronic rhinosinusitis (CRS), asthma and aspirin sensitivity (FIGURE 1) [5,6].

Despite the potent effects of steroids, the treatment of NPs remains controversial and sometimes frustrating for both patients and physicians owing to insufficient responses. Many patients undergo extensive medical management and multiple surgeries, yet they continue to relapse. The objectives of the management of NPs are to eradicate NPs from nasal and sinusal cavities, eliminate symptoms, reduce exacerbations of CRS and prevent recurrence. The treatment of NPs has been the topic of frequent controversial debates for many decades. Most authors and international guidelines generally suggest that first-line treatment should be based on a medical approach (long-term intranasal steroids and short-term systemic steroids). Surgical procedures are often viewed as adjunctive to medical therapy. Wynn and Har-El demonstrated that, despite pre- and postoperative nasal and systemic steroid treatment in the majority of patients, 60% developed recurrent polyposis, 47% were advised to undergo revision surgery

and 27% subsequently underwent revision surgery. History of previous sinus surgery, allergy or asthma predicted higher recurrence [7].

LT production

Leukotrienes are inflammatory mediators, previously known as the slow-reacting substances of anaphylaxis, produced by a number of cell types, including mast cells, eosinophils, basophiles, macrophages and monocytes. Synthesis of these mediators results from the cleavage of AA in cell membranes. They exert their biologic effects by binding and activating specific adaptors. This occurs in a series of events, which lead to the contraction of the human airway smooth muscle, cell chemotaxis and increased vascular permeability [8].

Cysteinyl LTs (cysLTs) are potent proinflammatory mediators produced from AA through the 5-lipoxygenase (5-LO) pathway. They exert important pharmacological effects by interaction with at least two different receptors: cysLT1 and cysLT2. cysLT1 mediates sustained bronchoconstriction, mucus secretion and edema in the airways. Selective antagonists of cysLT1 approved for the treatment of asthma block the proasthmatic effects of cysLT1. Experiments in mice that are deficient in cysLT2, or that overexpress cysLT2 in the lungs, indicate that cysLT2 does not mediate bronchoconstriction but, rather, contributes to inflammation, vascular permeability and tissue fibrosis [9].

Leukotrienes consist of LTA₄, LTB₄, LTC₄, LTD₄ and LTE₄, and they were named because the apparent molecule was originally isolated from leukocytes and, therefore, its carbon backbone contains three double bonds in series, which constitutes a triene. By competitive binding to the cysLT1 receptor, LT-receptor antagonist drugs, such as montelukast, zafirlukast and pranlukast, block the effects of cysLTs, improving the symptoms of some chronic respiratory diseases, especially bronchial asthma and allergic rhinitis (FIGURE 2).

Leukotrienes act by binding to specific receptors of the rhodopsin class that are located on the outer plasma membrane of structural and inflammatory cells. Once ligated by the LT, these receptors interact with G proteins in the cytoplasm, thereby eliciting increases in intracellular calcium and reductions in intracellular cyclic AMP. These proximal signals activate downstream kinase cascades in ways that alter various cellular activities, ranging from motility to transcriptional activation [10].

In bronchi of patients with aspirin-intolerant asthma (AIA), whose asthma is characterized by increased production of cys-LTs, there is an overexpression of LTC₄ synthase. This phenomenon is explained, at least in part, by a genetic polymorphism of the LTC₄ synthase gene. A common promoter variant of the gene creates a predisposition to AIA by reinforcing the effector mechanism of bronchoconstriction. Aspirin challenge studies, coupled with estimation of LTC₄ synthase polymorphism and LTC₄ urinary excretion, point to some heterogeneity between patients with AIA [11].

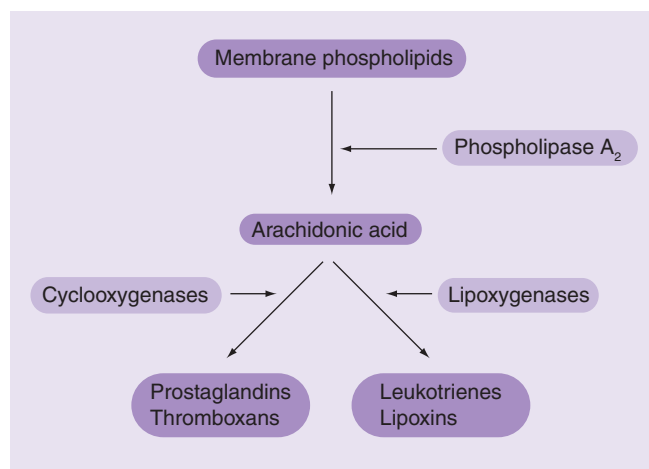


Figure 1. The two main metabolism pathways of arachidonic acid, produced from membrane phospholipids through the action of the enzyme phospholipase A₂.

Cyclooxygenases produce prostaglandins and thromboxans, while lipoxygenases produce leukotrienes and lipoxins.

LTs & NPs

Upper airway diseases, especially AIA, have been linked to changes in the AA cascade; however, the specificity of these changes and their relation to inflammatory reactions in these diseases still remain controversial.

Jung *et al.*, using high-performance liquid chromatography analysis, showed that the predominant metabolite in NPs was 15-hydroxyeicosatetraenoic acid (15-HETE), especially in patients with ASA. Levels of 15-HETE and prostaglandin (PGE)₂ were found to be higher in polyps from patients with a history of allergy than from nonallergic patients [8]. Cyclooxygenase (Cox) metabolites (thromboxane B₂, PGE₂ and 6-keto PGF₁) and LO metabolites (LTB₄ and LTC₄) were investigated in NPs, hypertrophic turbinates and nasal mucosa from 14 nonallergic, allergic rhinitis and ASA patients who underwent polypectomy. In NPs from allergic patients, significantly higher LTB₄ levels were observed, as well as a tendency to produce higher amounts of Cox products in comparison with nonallergic subjects, whereas, in turbinates of nonallergic patients, LT levels were significantly higher compared with those with allergic rhinitis. In ASA patients, a decreased Cox/LO ratio was found, supporting the hypothesis of an imbalance of AA metabolism in this syndrome [9].

Schmid *et al.* studied the production of PGE₂ and peptido-LTs (cysLT [LTC₄/D₄/E₄]) in nasal tissue, finding that cysLT in NPs from patients with AIA was found to be significantly higher than in normal mucosa from AIA patients and healthy controls. After bronchial provocation with lysine-ASA, a significant increase of cysLT was observed in each single tissue. NPs of AIA patients showed a significantly lower production of PGE₂ than normal mucosa from AIA patients

and controls [5]. PGE₂ has been shown to be a bronchoprotective agent when the bronchodilating effects of inhaled PGE₂ could be proved in aspirin-induced bronchoconstriction [14].

Picado *et al.* examined the expression of Cox-2 mRNA in healthy nasal mucosa and in NPs from patients with AIA and those with aspirin-tolerant asthma (ATA). They demonstrated no differences in the expression of Cox-1 mRNA expression from nasal mucosa and NPs from both ATA and AIA patients. However, Cox-2 mRNA expression in NPs from AIA patients was significantly underexpressed in comparison to polyps from ATA patients and nasal mucosa [6]. More recent studies have confirmed that there is an abnormal regulation of Cox metabolism in NPs from both aspirin-tolerant [15] and -intolerant [16,17] patients.

Perez-Navo *et al.* studied sinonasal tissue from patients with CRS associated with (n = 13) and without NPs (n = 11), with NP and aspirin sensitivity (n = 13), and normal nasal mucosa from healthy subjects (n = 8). They demonstrated that Cox-2 mRNA and PGE₂ concentrations were similar in the CRS and normal mucosa but significantly decreased in NP tissue, especially in the aspirin-sensitive group. LTC₄ synthase, 5-LO mRNA, LTC₄, LTD₄ and LTE₄ concentrations increased with disease severity among the patient groups. 5-LO and lipoxin A₄ concentrations were increased in all CRS groups compared with the normal mucosa, but were significantly downregulated in the aspirin-sensitive group when compared with the NP group. IL-5 and eosinophil cationic protein were increased in both groups of NP tissue compared with the normal mucosa and CRS groups and correlated directly with LTC₄, LTD₄ and LTE₄ concentrations and inversely with PGE₂ concentrations [18].

Therapy with montelukast & other anti-LT drugs in CRS and NP

Zileuton, a 5-LO inhibitor, inhibits the formation of LTs, whereas the lukast agents (montelukast, zafirlukast and pranlukast) are receptor antagonists. There have been a number of studies showing that these drugs can modify bronchospasm induced by exercise, particularly in aspirin-sensitive asthmatic patients. Anti-LTs improve the airway flow, decrease the need for rescue medication and diminish the symptoms of

asthma [19]. More recently, these drugs have been shown to be effective in allergic rhinitis, producing significant improvements in daytime nasal symptoms and in quality of life [20].

Results of recent studies indicate that there is a need for (larger) controlled trials of anti-LT treatment in CRS with or without NPs (TABLE 1). In a double-blind, placebo-controlled, crossover study, Dahlen *et al.* examined the effects of 6 weeks of treatment with the LK pathway inhibitor (zileuton 600 mg, four-times daily) in 40 patients with AIA [21]. There was an improvement in pulmonary function after treatment with zileuton, and higher morning and evening peak expiratory flow rate values on zileuton treatment compared with placebo. In addition, there was a significant return of sense of smell, less rhinorrhea and a trend for less nasal stuffiness, and higher nasal inspiratory flow during treatment with zileuton.

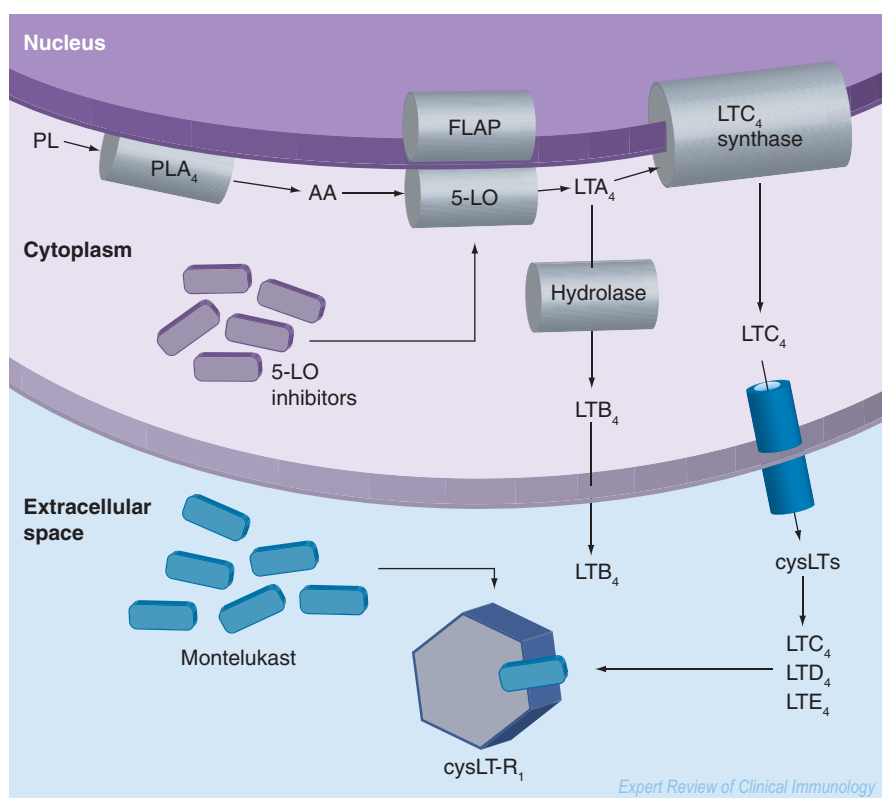


Figure 2. Cellular synthesis and production of leukotrienes. The enzyme phospholipase A₂ catalyzes the synthesis of AA from membrane PLs. The enzyme 5-LO, in association with the cofactor FLAP, is responsible for the conversion of free AA into LTA₄. The presence of a hydrolase converts LTA₄ in LTB₄, while the enzyme LTC₄ synthase catalyzes the production of LTC₄ from LTA₄. LTC₄ passively diffuses from cell cytoplasm to extracellular space, where it will gradually be converted in LTD₄ and LTE₄. The LTs LTC₄, LTD₄ and LTE₄, together named cysLTs, act on specific receptors (cysLT-R₁) expressed in structural and inflammatory cells; activation induces a variety of proinflammatory effects in the sinonasal mucosa. Some anti-LT drugs reduce LT synthesis by inhibiting 5-LO production, while montelukast and other LT-receptor antagonists reduce the proinflammatory effect of LTs in many cells by blocking the cysLT-R1 receptor.

5-LO: 5-lipoxygenase; AA: Arachidonic acid; cysLT: Cysteinyl-leukotriene; FLAP: 5-lipoxygenase activating protein; LT: Leukotriene; PL: Phospholipid.

Table 1. Studies using montelukast and other antileukotriene drugs in the treatment of nasal polyposis.

Study	Drugs	Patients (n)	Duration of treatment	Effects on symptoms	Other effects	EBM level	Ref.
Dalhen (1998)	Zileuton vs placebo	40	6 weeks	Smell loss and rhinorrhea significantly improved	Pulmonary function improvement	IIb	[21]
Ulualp (1999)	Zafirlukast vs zileuton	18	12 months	Improved symptom scores and nasal endoscopy	Less nasal crusting and erythema	III	[22]
Parnes (2000)	Zafirlukast vs zileuton	36	7 months	Improved symptom scores and decreased polyp size	No more revision surgery	III	[23]
Kutting (2000)	Montelukast + oral steroids	9	Not shown	Improved nasal obstruction and rhinorrhea. No evidence of recurrence	Resolution of paranasal sinus MRI findings	III	[24]
Di Rienzo (2000)	Montelukast vs mometasone	40	6 months	Absence of local recurrence and good nasal patency	Reduction steroids and bronchodilator inhalants	IIb	[25]
Ragab (2001)	Montelukast + local steroids	44	3 months	Clinical subjective improvement	Asthma improvement	IIb	[26]
Grundmann (2001)	Montelukast	18	Not shown	Improved pulmonary symptoms and significant reduction of polyps	Improved pulmonary symptoms	III	[27]
Mostafa (2005)	Montelukast vs beclomethasone	40	12 months	Significant reduction in symptom scores. No difference in recurrence	No difference in rescue medications	IIa	[28]
Kieff (2005)	Montelukast + local steroids	24	3 months	Improved symptom scores	Reduction of nasal polyps eosinophilia	III	[29]

EBM: Evidence-based medicine.

Ulualp *et al.* studied 18 patients who had all undergone previous sinus surgery [22]. In total, 16 received zafirlukast and two received zileuton. They were evaluated by questionnaires and postoperative sinus endoscopies. After a follow-up of several months to 1 year, the overall benefit on the questionnaire was positive in 12 out of 15 patients (80%), consistent with the change in symptom scores. The endoscopic findings demonstrated no abnormalities in eight (53%), nasal crusting in six (40%) and erythema with nasal crusting in one patient (7%) out of the 15 subjects. In this uncontrolled study, the authors concluded that anti-LT therapy seemed to be an effective treatment for most patients whose symptoms of CRS persist following sinus surgery.

Parnes and Chuma investigated the effect of anti-LT added to the standard treatment in 36 patients with CRS with or without NPs [23]. In total, 26 received zafirlukast, five zileuton and the remaining five switched from zafirlukast to zileuton. Statistically significant improvement was noted with respect to headache, facial pain and pressure, ear discomfort, teeth pain, purulent nasal discharge, postnasal drip, nasal congestion and obstruction, olfaction and fever in those patients receiving zafirlukast or zileuton. Overall improvement was noted by 72% of the patients and side effects occurred in 11%. An objective improvement, or at least stabilization, of NP was seen in 50% of the patients.

Kutting *et al.* evaluated the effect of montelukast (10 mg daily) associated with oral steroids (oral methylprednisolone 40 mg) in nine patients with severe NPs [24]. Seven patients (78%) presented with symptomatic improvement (nasal obstruction and rhinorrhea) and four (44%) were free of nasal symptoms. Endoscopic examination demonstrated no evidence of NP recurrence in five (56%) patients, one (11%) with NP reduction and three (33%) without changes. Paranasal sinus MRI findings revealed resolution of the sinus opacification in four (44%) patients. There were no further side effects of montelukast.

In total, 40 patients suffering from ASA syndrome and NPs were studied prospectively by Di Rienzo *et al.* All underwent microendoscopic surgery followed by treatment with either montelukast (10 mg daily) or mometasone furoate (100-µg daily nasal sprays) with loratadin (10 mg daily) for 6 months. The results obtained in patients treated with montelukast were analogous with those obtained in the second group and, during follow-up, all patients showed total absence of any local recurrence, good nasal patency and no significant nasal symptom score on the questionnaire. In no case did the comparative CT, performed after 7 months, show any signs of recurrence. Patients receiving montelukast reported a significant reduction in the use of steroids and bronchodilator inhalants during the course of the study.

compared with the second group; indeed, the number of asthmatic episodes dropped and they reported an improvement in quality of life [25].

Early open studies suggested that anti-LTs might be of benefit in the treatment of NP both from ATA and AIA asthmatic patients. Ragab *et al.* investigated the response to montelukast, as an add-on therapy to topical and inhaled steroids, in patients with NPs and AIA or ATA [26]. Clinical subjective improvement in NP occurred in 64% of ATAs and 50% of AIAs; asthma improvement occurred in 87% ATAs and 61% of AIAs. Objective changes in peak flow occurred only in ATAs, while acoustic rhinometry, nasal inspiratory peak flow and nitric oxide levels did not change. They concluded that the clinical response to montelukast appeared to be more impressive with respect to asthma than NP, possibly suggesting that LTs are more relevant in the lower than in the upper airway.

Grundmann and Topfner studied 18 patients with AIA diagnosed by oral provocation and treated with montelukast after undergoing sinus surgery [27]. The authors used endoscopic evaluations and determined serum eosinophilic cationic protein (ECP) levels. There was a significant reduction of the serum ECP levels with a beneficial effect on the nasal and pulmonary symptoms, as well as a significant reduction of polyps noted on endoscopic examination.

A prospective, double-blind study on 40 patients compared the effects of the LT receptor antagonist montelukast (10 mg daily) and nasal beclomethasone (400 µg daily) on the postoperative course of patients with NPs [28]. There was a significant reduction in symptom scores in both groups between these two postoperative treatments in the year following surgery. There was no difference in the recurrence rate or in the need for rescue medications between both groups throughout the study period.

In total, 24 patients with symptomatic NP and nonallergic or perennial rhinitis who were undergoing chronic nasal steroid therapy were evaluated for response to adjunctive oral montelukast therapy. The NPs were submitted to biopsy to determine their degree of eosinophilia. Kieff *et al.* concluded that montelukast appears to be beneficial for some patients with NP [29]. Patients with perennial allergies and NPs seem more likely to respond to the treatment than those with nonallergic NP.

Anti-LTs are well tolerated and have few side effects. Headaches and gastrointestinal side effects are the most common, but these are rarely severe enough to cause discontinuation of therapy. The major concern is the development of Churg–Strauss syndrome, which has been associated with all anti-LTs; however, it is not clear whether this is an effect of tapering the oral steroid dose in patients who already have this syndrome, rather than a direct effect of the drug [30]. There are several case reports of Churg–Strauss syndrome developing in patients who have not been treated with corticosteroids, suggesting that it may be a direct effect of the anti-LTs [31].

Expert commentary

Anti-LTs are indicated in the treatment of asthma and allergic rhinitis. With the demonstration of increased LT production in the polyps, anti-LTs are increasingly being studied in the management of NPs. The results of these studies show a positive trend in the use of anti-LTs in CRS with NPs.

Five-year view

There is an urgent need for larger randomized, placebo-controlled trials of LT receptor antagonists in patients with CRS with or without NPs and in patients with or without aspirin sensitivity. In addition, genetic studies are also needed to identify responder patient's tributary for anti-LT treatment. The role of anti-LTs in the postoperative management is still unclear and scientific studies will also be performed. The recommendation of anti-LT drugs may represent, in the near future, an additional therapeutic option for patients suffering from CRS and NPs.

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Key issues

- Upper airway diseases, especially aspirin-hypersensitivity syndrome, have been linked to changes in the arachidonic acid cascade and metabolism.
- There is an abnormal regulation of cyclooxygenase metabolism in nasal polyps from both aspirin-tolerant and -intolerant patients. Due to this, an imbalance between cysteinyl-leukotrienes (increased) and cyclooxygenase-2 and prostaglandin E₂ (decreased) exists in nasal polyps, mainly when associated with aspirin sensitivity.
- Antileukotrienes are indicated in the treatment of allergic rhinitis and bronchial asthma.
- Recent studies have demonstrated that antileukotrienes have some efficacy in the treatment of chronic rhinosinusitis with or without nasal polyps, especially in patients with aspirin hypersensitivity.
- Finally, there is an urgent need for randomized, placebo-controlled trials using leukotriene receptor antagonists in the treatment of patients with chronic rhinosinusitis with or without nasal polyps and with or without aspirin sensitivity.

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