

Aspirin-induced asthma: Advances in pathogenesis and management

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In some patients with asthma, aspirin (ASA) and all non-steroidal anti-inflammatory drugs that inhibit cyclooxygenase enzymes (cyclooxygenase-1 and -2) precipitate asthmatic attacks and naso-ocular reactions. This distinct clinical syndrome, called aspirin-induced asthma (AIA), is characterized by a typical sequence of symptoms, intense eosinophilic inflammation of nasal and bronchial tissues, combined with overproduction of cysteinyl-leukotrienes (Cys-LTs). At baseline, cys-LT urinary excretion is augmented, and ASA administration leads to its further temporary increase. After ASA challenge, cys-LTs are released into nasal and bronchial secretions and can be collected in the urine. LTC₄ synthase, the terminal enzyme for cys-LT production, is markedly overexpressed in eosinophils and mast cells from bronchial biopsy specimens of most patients with AIA. An allelic variant of LTC₄ synthase that enhances enzyme transcription is associated with AIA. Avoiding ASA and nonsteroidal anti-inflammatory drugs does not prevent progression of the inflammatory disease. Corticosteroids continue to be the mainstay of therapy, and anti-LT drugs are also indicated for treatment of the underlying disease. After ASA desensitization, daily ingestion of high doses of ASA reduces inflammatory mucosal disease symptoms, particularly in the nasal passages, in most patients with AIA. (*J Allergy Clin Immunol* 1999;104:5-13.)

Key words: Asthma, aspirin-induced asthma, cyclooxygenase enzymes, 5-lipoxygenase enzymes, leukotrienes, leukotriene C₄ synthase, aspirin desensitization

Shortly after aspirin (ASA) was introduced into therapy 100 years ago, ASA was implicated as the cause of violent attacks of asthma. In 1922, the association of ASA sensitivity, asthma, and nasal polyposis was described by Widal et al,¹ and this clinical entity, subsequently named "aspirin triad," was popularized by the studies of Samter and Beers.² It constitutes a remarkable model for investigating mechanisms that operate in asthma, rhinitis, and nasal polyposis. The recent introduction

Abbreviations used

ASA:	Aspirin
AIA:	Aspirin-induced asthma
ATA:	Aspirin-tolerant asthma
BAL:	Bronchoalveolar lavage
COX-1:	Cyclooxygenase-1 enzyme
COX-2:	Cyclooxygenase-2 enzyme
Cys-LT:	Cysteinyl leukotriene
LO:	Lipoxygenase
LT:	Leukotriene
NSAID:	Nonsteroidal anti-inflammatory drug

of anti-leukotriene (anti-LT) drugs³ has amplified interest in this syndrome. Here we discuss advances in the pathogenesis and management of aspirin-induced asthma (AIA), starting with a brief presentation of its clinical features.

DEFINITION AND CLINICAL PRESENTATION

AIA, also called aspirin-sensitive or aspirin-intolerant asthma, is an aggressive mucosal inflammatory disease combined with precipitation of asthma and rhinitis attacks after ingestion of ASA and most nonsteroidal anti-inflammatory drugs (NSAIDs).⁴⁻⁷ AIA affects about 10% of adults with asthma, more often women than men.⁸ Familial occurrence is quite rare, and the disease is infrequently found in asthmatic children.⁸

In most patients symptoms of rhinitis first occur during the third decade, often after a viral respiratory illness. Over a period of months, chronic nasal congestion, anosmia, and rhinorrhea develop. Physical examination often reveals nasal polyps. Bronchial asthma and sensitivity to ASA usually develop next. After ingestion of ASA or an NSAID, an acute asthma attack occurs within 3 hours, usually accompanied by profuse rhinorrhea, conjunctival injection, periorbital edema, and sometimes a scarlet flushing of head and neck. ASA is a common precipitant of life-threatening attacks of asthma.⁹ In a large survey 25% of asthmatic patients requiring emergency mechanical ventilation were found to have AIA.¹⁰

Aggressive nasal polyposis and asthma run a protracted course, despite the avoidance of ASA and cross-reacting drugs. Blood eosinophil counts are raised, and

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eosinophils are present in nasal mucosa and bronchial airways. Although at one time AIA was thought to not occur in atopic patients, positive skin test responses to common aeroallergens are actually similar in patients with AIA and those with other types of asthma.¹¹

Although clinical history might raise the suspicion of AIA, the diagnosis can be established with certainty only by ASA provocation tests. There are 3 types of provocation tests, depending on the route of ASA administration: oral, inhaled, and nasal. Oral challenge tests are most commonly performed; in most patients threshold doses evoke positive respiratory reactions after ingesting 30 to 150 mg of ASA (average, 60 mg).⁵ In inhalation tests aerosols of L-lysine acetylsalicylic acid are administered.¹² Inhalation challenge can be completed in 4 hours, but reactions are usually restricted to the lower respiratory tract. Nasal provocation testing¹³ is an attractive research model and can be also used as a diagnostic procedure in outpatients; its value, however, is limited by reduced sensitivity when compared with oral or inhalational provocation testing. With few exceptions, once ASA sensitivity develops, it remains for the rest of the patient's life.

PATHOGENESIS

The futile search for an allergic mechanism

Clinical symptoms precipitated by ASA or NSAIDs in patients with AIA are reminiscent of immediate hypersensitivity reactions. Therefore an underlying antigen-antibody mechanism has been suggested and investigated. However, skin test responses with ASA-lysine have been negative, and numerous attempts to demonstrate specific antibodies against ASA or its derivatives were unsuccessful.¹⁴ Neither differences in bioavailability of ASA nor the formation of salicylic acid seem to contribute to ASA-induced respiratory reactions.¹⁵ Furthermore, in patients with AIA, asthmatic attacks can be precipitated not only by ASA but also by other NSAIDs with distinct chemical structures, frequently on first exposure to the new NSAID. All of these facts make immunologic cross-reactivity most unlikely.

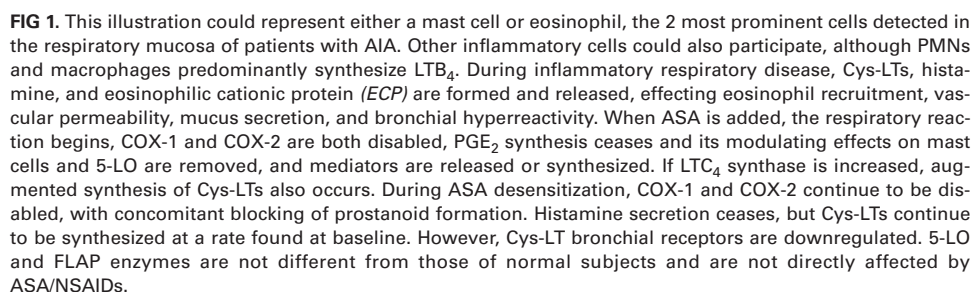
The cyclooxygenase pathway

The cyclooxygenase (COX) theory¹⁶ proposes that precipitation of asthma attacks by ASA and NSAIDs is not based on antigen-antibody reactions but by the shared pharmacologic actions of ASA/NSAIDs,¹⁷ namely specific inhibition in respiratory cells of intracellular COX enzymes (Fig 1). The original observations by Szczeklik et al in 1975,^{18,19} that drug cross-reactivity can be predicted on the basis of each NSAID's *in vitro* inhibition of COX, have been consistently reaffirmed over the years.^{20,21} After ASA desensitization, cross-desensitization to other NSAIDs that inhibit COX also occurs.²⁰ These constitute the major facts supporting the COX theory, the additional evidence for which has been summarized elsewhere.¹⁶

The COX enzymes, which appear to be central to the

mechanism of ASA sensitivity, exist in at least 2 isoforms, COX-1 and COX-2, which are encoded by distinct genes. Both isoforms are actually coenzymes with a peroxidase, forming the complete enzyme PGH₂ synthase. COX-1, the constitutive form, is a housekeeping hormone that is widely distributed in most mammalian cells. COX-2 is induced during inflammation and enhances synthesis of inflammatory prostanooids. Both enzymes are expressed in normal human respiratory epithelium²² and are not quantitatively upregulated in bronchi of patients with stable asthma and chronic bronchitis. By using immunostaining techniques, the overall expression of COX-1 and COX-2 is similar in bronchial biopsy specimens obtained from ASA-tolerant and ASA-intolerant asthmatic patients.²³⁻²⁴ Furthermore, after bronchial challenge with ASA-lysine, cells in bronchoalveolar lavage (BAL) fluid, staining for COX-1 or COX-2, were not found to be increased preferentially in patients with AIA.²⁴ Low doses of ASA, indomethacin, and piroxicam precipitate asthmatic attacks in sensitive patients and inhibit both enzymes but are much more potent inhibitors of COX-1 than COX-2. Other salicylates, which are well tolerated by patients with AIA, are practically devoid of effect on COX-1 in intact cells but have half of the potency of ASA in inhibiting COX-2 in certain cell lines. Nimesulide and meloxicam, drugs known to inhibit COX-2 substantially more than COX-1, are well tolerated by ASA-sensitive asthmatic subjects when given average therapeutic doses but cause rhinorrhea and mild asthma attacks when ingested in higher doses.^{25,26} The recent introduction into clinical practice of highly selective inhibitors of COX-2, namely celecoxib and rofecoxib,²⁷ which theoretically should not cross-react with ASA because of preservation of constitutive PGE₂, will provide an interesting tool for further determining the role of COX isoforms in AIA.

When segmental bronchial challenges with ASA were performed in patients with AIA and aspirin-tolerant asthma (ATA), and COX products were measured in BAL fluid 15 minutes after installation of ASA-lysine, a marked difference became apparent.²⁸ ASA significantly depressed formation of PGE₂ and thromboxane B₂ in both groups; however, mean levels of PGD₂, PGF_{2α}, and 9α,11β-PGF₂ were not depressed in BAL fluid from subjects with AIA but were significantly decreased only in the control (ATA) patients. In individual subjects with AIA, PGD₂ levels varied in response to ASA challenge from marked increase to depression.²⁸ Histamine and eosinophil cationic proteins were also preferentially released into the BAL fluid of patients with AIA, but changes in mean levels barely missed being statistically significant.²⁸ Activated mast cells are a likely source of histamine and PGD₂. The role of mast cells in the pathogenesis of AIA has been investigated by Fisher et al²⁹ and Warren et al.³⁰ The latter investigators reported that segmental bronchial challenge with indomethacin led to a rise in PGD₂ and histamine in BAL fluid from 3 patients with AIA when compared with BAL fluid from 3 patients with ATA. A modest increase was seen in uri-



Thus the COX response to ASA was selectively altered in patients with AIA. Such alterations may result from an acquired change in the COX gene or genes, perhaps as a consequence of a latent viral infection.³³ Such an alteration in the COX molecule, specific for patients with AIA, has not been identified. Currently available

immunohistochemical staining may not be able to detect subtle changes in amino acid sequences or configuration of COX molecules. However, an altered COX-1 or COX-2 enzyme might be more vulnerable to ASA or could produce unknown metabolites that stimulate cysteinyl leukotriene (Cys-LT) production. Alternatively, a major signal for enhanced 5-lipoxygenase (LO) activity stems from removal of PGE₂ after the inhibitory effects of ASA/NSAIDs on COX-1 and COX-2.³⁴ PGE₂ in many

cells, including endothelial and epithelial cells of the respiratory tract, has profound regulatory effects on other inflammatory systems³⁵: (1) it reduces LT biosynthesis through inhibition of 5-LO³⁵⁻³⁷; (2) it inhibits cholinergic transmission, which can be disregulated by chronic viral infection³⁸; (3) it prevents discharge of granular mediators from mast cells³⁷; and (4) it prevents ASA-precipitated bronchoconstriction and the expected rise in urinary LTE₄ when given by means of inhalation to patients with AIA³⁹ or as an oral PGE₁ analog (misoprostol).⁴⁰ Because ASA destroys COX-1 and COX-2 in all cells, the initiating stimulus for ASA-induced respiratory reactions appears to be the interruption of synthesis of PGE₂ and its modulating effects on inflammatory cells. Thus disruption of synthesis of some prostanoids (PGE₂ and PGI₂) and/or diversionary synthesis of others after interactions between ASA/NSAIDs and COX enzymes seem to be crucial events in the pathogenesis of ASA-induced respiratory reactions.^{16,20,21} Why the interruption of PGE₂ synthesis by ASA/NSAIDs does not induce respiratory reactions in all humans, or at least all asthmatic subjects, is the crux of the riddle in understanding ASA-induced respiratory reactions. Intuitively, either COX enzymes are the same in patients with AIA and ATA and another set of pathologic conditions must coexist in the 5-LO pathway, or COX enzymes are different or differentially susceptible to ASA/NSAIDs only in patients with AIA.

The lipoxygenase pathway

Over the last few years, Cys-LTs have emerged as major mediators in AIA (Fig 1). Most patients with AIA excrete 2- to 10-fold higher amounts of LTE₄ in urine than asthmatic subjects who tolerate ASA. There is, however, some overlap between the groups, and no correlation was found between urinary LTE₄ and histamine PD₂₀ or baseline FEV₁ values.⁴¹ Either oral or inhalational ASA challenges resulted in temporary, although significant, increases in urinary LTE₄ excretion.⁴¹⁻⁴³ Cys-LTs are also released into nasal secretions after oral or nasal challenge with ASA⁴⁴⁻⁴⁷ and into bronchi after challenge with ASA-lysine.²⁸ This is accompanied by simultaneous inhibition of thromboxane B₂ and PGE₂, whereas 15-LO metabolites remain unaltered.⁴⁶ When blood leukocytes obtained from patients with AIA and prestimulated with IL-3 were incubated with ASA, together with C5a, they released more cys-LTs when compared with normal leukocytes.⁴⁸ Thus as shown in Fig 1, Cys-LTs are continuously and aggressively synthesized in patients with AIA before any exposure to ASA/NSAIDs, and during ASA-induced reactions, marked acceleration of synthesis occurs. Thus patients with AIA differ significantly from other asthmatic and normal subjects with respect to their increased synthesis of Cys-LTs at baseline. Because synthesis of cys-LTs is already underway, the release of the braking effect of PGE₂ correlates with augmented synthesis during the reaction.

The terminal enzyme for Cys-LT production is LTC₄

synthase (Fig 1), the gene of which has been localized on chromosome 5q, telomeric to other candidate asthma genes, including IL-3, IL-4, IL-5, and GM-CSF.⁴⁹ The expression of LTC₄ synthase was 5-fold higher in bronchial biopsy specimens from patients with AIA than from patients with ATA and 19-fold higher than in biopsy specimens from normal control subjects. By contrast, expression of other LT pathways/enzymes (5-LO, 5-LO activating protein, and LTA₄ hydrolase) was similar in all subject groups.²⁴ Increased LTC₄ synthase expression in biopsy specimens from patients with AIA was the only enzyme or cell marker that correlated significantly with bronchial hyperresponsiveness to inhaled ASA-lysine,²⁴ a definitive clinical measure of AIA.

If Cys-LTs are common mediators of bronchoconstriction in all asthmatic subjects and mucosal inflammation in allergic rhinitis, why is there only a subset of patients who are ASA sensitive? The answers elude us, but certain possibilities have begun to emerge. As indicated earlier, the protective effects of PGE in downregulating mast cells and 5-LO are intuitively important in the ultimate synthesis of Cys-LTs after ASA interrupts synthesis of prostanoids.

Increased availability of the LTC₄ synthase enzyme may be augmented by genetic upregulation. The promoter region of the enzyme is complex and predicts interaction with many transcription enhancers. LTC₄ synthase is present in eosinophils and mast cells. Expression of LTC₄ is variable, even in the same cell line. Recently, the genetic polymorphism of the 5-untranslated region of LTC₄ synthase has been described.⁵⁰ It consists of 2 common alleles corresponding to the A to C transversion of nucleotide 444 upstream of the translation start. The C₄₄₄ allele is 60% more common in patients with AIA than in asthmatic subjects insensitive to aspirin. Patients with AIA have upregulated LTC₄ synthase mRNA expression in blood eosinophils, and increased gene transcripts are most pronounced in carriers of the C₄₄₄ allele.⁵¹ Although there is no relationship between LTC₄ synthase polymorphism and urinary LTE₄ excretion at baseline, provocation with ASA leads to dramatic increases in urinary LTE₄ in carriers of the C₄₄₄ allele.⁵² The allele associated with AIA has an additional transcription activator-binding motif. Facilitated inducibility of the enzyme may thus promote onset of ASA-induced disease and enhancement of ASA-induced respiratory reactions. However, almost 30% of patients with AIA do not have a predisposing variant of the LTC₄ synthase gene, whereas 25% of control subjects do have it, apparently without consequences to their health. Such a finding is common in studies on genetic predisposition to multifactorial diseases and is predictable on the basis of non-Mendelian low inheritance of AIA. However, studies are currently underway in a more heterogeneous population of patients with AIA to determine whether the promoter gene for LTC₄ synthase is proportionately distributed. If COX enzymes in patients with AIA are similar to those found in patients with ATA, we must look at potential reasons why overproduction of Cys-LTs occurs in patients with AIA. In some patients

with AIA, overexpression of LTC₄ synthase could be such a differentiating finding.

The discordance between the genetic predisposition and AIA requires further studies on triggering factors, such as intermittent or persistent viral infections. The genetic predisposition may also result from polygenic effects, in which other elements of signaling, like cys-LT receptors, play a significant role.⁵³ Enhanced responsiveness of Cys-LT receptors to inhaled LTE₄ has been identified in patients with AIA,⁵³ and this phenomenon augments the effects of synthesized LTs. Newly described interactions of lipoxins and Cys-LT signaling pathways⁵⁴ may have a yet unknown relevance in the pathogenesis of AIA. By contrast, genetic variations of 5-LO, the first enzyme in the LT pathway, have not been shown to be different in subjects with AIA and thus do not appear to contribute to ASA-induced disease or modulate reactions found only in patients with AIA.⁵⁵

Chronic inflammation of the airways

The airways of patients with AIA show signs of persistent inflammation, with marked eosinophilia, epithelial disruption, cytokine production, and upregulation of adhesion molecules.^{56,57} In bronchial biopsy specimens, eosinophils are 4-fold more numerous than in subjects with ATA and 15-fold more numerous than in biopsy specimens of normal mucosa.²⁴ There is a tendency for higher counts of CD68⁺ macrophages, whereas counts of T lymphocytes do not differ from other types of asthma or control subjects. Both increase⁵⁶ and suppression²⁴ of mast cell numbers, as compared with normal control subjects, have been reported, with the discrepancies probably reflecting mast cell activation and disruption.

Eosinophil infiltration of airway tissue appears to be a central feature of AIA. Eosinophil cationic protein is found in BAL fluid and increases after ASA-lysine segmental challenge in patients with AIA.²⁸ The airway expression of IL-5, known to be involved in the recruitment, activation, maturation, and perpetuation of survival of eosinophils, is markedly increased in patients with AIA.^{24,58} Immunohistochemical staining of bronchial biopsy specimens shows that eosinophils are the predominant cells containing LTC₄ synthase, the essential enzyme for Cys-LT synthesis. Thus sheer numbers of eosinophils, loaded with normally expressed or increased Cys-LT enzymes, may be responsible for overproduction of total Cys-LTs, a differentiating feature of AIA. Two chemokines, RANTES and eotaxin, are present in nasal mucosa and polyp tissues, and their local expression is upregulated in individuals with chronic sinusitis.⁵⁹ Their role in the pathogenesis of eosinophilic inflammation in AIA remains to be established.

Persistent airway inflammation in AIA could result from non-IgE-mediated reactions to an endogenous or exogenous antigen or virus. These possibilities are supported by the finding of elevated markers of autoimmunity,⁶⁰⁻⁶² enhanced IgG₄ synthesis,⁶³ and HLA association with AIA.⁶⁴ A latent virus infection could³³ (1) modify the genetic message for COX molecules, altering

response to NSAIDs by synthesizing unknown metabolites that stimulate LT production; (2) evoke an immunologic response, perhaps dominated by specific cytotoxic lymphocytes and eosinophils, previously suppressed by PGE₂; or (3) leave DNA fragments in native DNA, which might direct synthesis of altered enzymes.

PREVENTION AND TREATMENT

The general rules concerning treatment of AIA do not differ from the published guidelines on the management of asthma. Most patients with AIA have moderate or severe persistent asthma. However, patients with AIA whose sinusitis is in remission may have mild asthma. These observations were recently confirmed by a multicenter study performed by participants of the European Network on Aspirin-Induced Asthma. Among 365 patients with AIA in the European Network on Aspirin-Induced Asthma study,⁶⁵ 79% were receiving long-term oral or inhaled corticosteroid therapy. Half of the subjects were treated with systemic corticosteroids, and 32% were treated with inhaled corticosteroids alone, although in relatively high doses (800 to 2000 µg per day). Nearly 20% of patients were treated with intravenous corticosteroids during the year preceding registration in the database. In sporadic cases, cyclosporin may help reduce the need for higher doses of corticosteroids. However, its clinical effects are negligible, and side effects are of concern.⁶⁶

There are, however, some important differences in the care of patients with AIA. First, to prevent life-threatening reactions, patients with AIA should avoid ASA, all products containing ASA, and other analgesics that inhibit COX. Thus the education of physicians, pharmacists, and patients is extremely important. The patient should receive a list of drugs that are contraindicated, preferentially with both generic and trade names (Table I).

If necessary, patients can usually take acetaminophen (paracetamol). A cross-reaction prevalence of 34% after ingestion of 1000 and then 1500 mg of acetaminophen was reported in patients with AIA.⁶⁷ It is generally safer not to exceed a dose of 1000 mg of acetaminophen at the beginning of therapy but to administer small doses and monitor the patient for 3 hours. Patients with AIA can also safely receive sodium salicylate, salicylamide, choline magnesium trisalicylate, benzydamine, chloroquine, azapropazone, and dextropropoxyphen. These drugs are devoid of anti-COX activity or are weak COX-2 inhibitors. Unfortunately, they are poor analgesics and have only minimal anti-inflammatory effects. Nimesulide and meloxicam, drugs known to inhibit COX-2 more than COX-1, induced mild bronchial obstruction, although only at high doses.^{25,26,68} Selective inhibitors of COX-2 have not been studied with respect to cross-reactivity with ASA but theoretically should be safe for patients with AIA because constitutive COX-1 will continue to synthesize the protective prostanoid, PGE₂.

There exists, however, another strategy to administer ASA or NSAIDs to patients with AIA. A state of ASA tolerance can be induced and maintained by aspirin

TABLE I. NSAIDs that cross-react with ASA in respiratory reactions

	Generic names	Brand names
Inhibitors of both COX-1 and COX-2: On first exposure to the drug, cross-reactions with low provoking doses	Piroxicam	Feldene
	Indomethacin	Indocin
	Sulindac	Cilnoril
	Tolmetin	Tolectin
	Ibuprofen	Motrin, Rufen, Advil
	Naproxen	Naprosyn
	Naproxen sodium	Anaprox, Aleve
	Fenoprofen	Nalfon
	Meclofenamate	Meclomen
	Mefenamic acid	Ponstel
	Flurbiprofen	Ansaid
	Diflunisal	Dolbid
	Ketoprofen	Orudis, Oruval
	Diclofenac	Voltaren, Cataflam
	Ketoralac	Toradol
	Etodolac	Lodine
	Nabumetone	Relafen
	Oxaprozin	Daypro
Poor inhibitors of COX-1 and COX-2: a small percentage of patients with AIA cross-react with high dose of these drugs	Acetaminophen	Tylenol
	Salsalate	Disalcid
Relative inhibitors of COX-2 and minor inhibition of COX-1: Only cross-react at high doses, and respiratory reactions are relatively minor	Nimesulide	(available outside US)
	Meloxicam	(available outside US)
Selective inhibitors of COX-2: In theory should not cross-react but have not been studied	Celecoxib	Celebrex
	Rofecoxib	Vioxx

desensitization. Small incremental oral doses of ASA are ingested over the course of 2 to 3 days until 400 to 650 mg of ASA is tolerated. ASA can then be administered daily, with doses of 80 to 325 mg used to maintain desensitization. After each dose of ASA, there is a refractory period of 2 to 5 days, during which ASA and other COX inhibitors can be taken with impunity. This is important for patients with AIA who have degenerative joint diseases, rheumatic diseases, and headaches and as a preventive measure for treatment of vascular diseases.

During the state of ASA desensitization, if ASA doses are increased to 650 mg and taken twice daily continuously, the patients usually experience improvement in their chronic respiratory symptoms and signs, especially in the nose.^{69,70} There are no clear-cut indications for ASA desensitization treatment, but nasal inflammatory disease appears to respond best. The ideal candidate for this treatment is a patient with AIA who has just completed sinus/polyp surgery. ASA desensitization treatment was shown to delay recurrence of nasal polyp formation by an average of 6 years.⁷⁰ The mechanism of ASA desensitization in patients with AIA is only partially understood. It may lead to reduction of airway responsiveness to LTE₄ because of downregulation of Cys-LT receptors,⁵³ which reduces receptor responsiveness to the same burden of Cys-LTs. At acute desensitization, urinary LT levels are the same as baseline levels and are

therefore clearly available for stimulation of cys-LT receptors. In a study by Juergens et al,⁷¹ desensitization to ASA followed by long-term treatment with ASA given twice daily resulted in decreased peripheral monocyte LTB₄ production and continued inhibition of COX enzymes. Patients maintained for months in a state of ASA desensitization still respond to oral ASA challenge with a rise in LTE₄ urinary excretion, although the responses were blunted when compared with the original ASA challenges, and the patients were all asymptomatic.⁷²

A drug and a dye should be mentioned when discussing drug cross-reactivity in AIA. Intravenous hydrocortisone hemisuccinate may sporadically provoke bronchoconstriction in patients with AIA.⁷³ In a study by Feigenbaum et al,⁷⁴ only 1 of 44 ASA-sensitive asthmatic subjects reacted to both hydrocortisone succinate and methylprednisolone succinate. Coincidental IgE-mediated reactions to the succinate molecule, rather than cross-sensitivity, was supported by the fact that readministration of hydrocortisone succinate during the ASA-desensitized state continued to induce a respiratory reaction in this patient. Tartrazine, a yellow azo dye used for coloring foods, drinks, drugs, and cosmetics was frequently cited in older reports as a cause of bronchospasm.² As early as 1979, Weber et al⁷⁵ reported that in their ASA-sensitive asthmatic patients, reduced lung function values

after tartrazine challenges resulted from withholding essential anti-asthmatic controller medications, rather than reactions to tartrazine. More recently, extensive and controlled studies indicate that tartrazine intolerance is extremely rare among ASA-sensitive asthmatic subjects.^{76,77} Because tartrazine does not inhibit COX,⁷⁸ it is likely that the rare tartrazine-induced reactions in patients with AIA are IgE mediated and coincidental rather than cross-reacting.

The anti-LT drugs have been introduced for treatment of AIA.³ Currently available drugs either inhibit LT synthesis by blocking 5-LO (ie, zileuton) or by blocking specific cys-LT receptors (ie, zafirlukast, montelukast, and pranlukast). Pretreatment with LT-modifying drugs attenuated ASA-provoked nasal and bronchial reactions in most, but not all, patients.⁷⁹⁻⁸² However, all studies were performed with prior established provoking doses of ASA. A recent study by Pauls et al⁸³ reported that higher therapeutic doses of ASA overcame protection from pretreatment with zileuton. In these 10 patients who were theoretically protected by zileuton, after challenge with the same or larger provoking doses of ASA, 4 of 10 experienced significant asthmatic reactions, and 10 of 10 experienced naso-ocular reactions.

Bronchodilation has also been observed after treatment with anti-LT drugs, indicating that cys-LTs have an effect on intrinsic airway tone in AIA. Two clinical trials with anti-LT drugs in patients with AIA have been concluded. In a Swedish-Polish double-blind, placebo-controlled, cross-over study, 40 patients with AIA received 6-week add-on treatment with zileuton (600 mg given 4 times daily).⁸⁴ While continuing baseline inhaled and systemic corticosteroids, zileuton provided acute and chronic improvement in pulmonary function measurements expressed both as increased FEV₁ values from baseline and higher morning and evening peak expiratory flow values compared with placebo-treated patients, despite a lowered requirement for rescue bronchodilators. Zileuton also diminished nasal dysfunction (remarkable return of smell, less nasal congestion, and a trend for less stuffiness and higher nasal inspiratory flow) and caused a small but distinct reduction in histamine-induced bronchoconstriction.

The Cys-LT receptor antagonist montelukast has been used in a double-blind, placebo-controlled, parallel-group, 4-week study in 80 patients with AIA whose symptoms were not fully controlled by treatment with inhaled or oral corticosteroids.⁸⁵ The patients received either oral montelukast 10 mg or placebo each night. Montelukast treatment significantly improved parameters of asthma control (weekly FEV₁, daily peak expiratory flow rate, and reduction in β -agonist use). Patients receiving montelukast had less nocturnal asthma and more asthma-free days and reported significant improvement in asthma-specific quality of life and global assessments. In rare cases of asthma, including patients with AIA, treatment with zafirlukast was associated with Churg-Strauss syndrome.^{86,87} It has been assumed that these patients already had eosinophilic vasculitis and sys-

temic steroid withdrawal during zafirlukast therapy, which led to reappearance of their disease. However, Churg-Strauss syndrome during zafirlukast treatment was recently reported in 2 patients who were not receiving systemic corticosteroids.⁸⁸

The β_2 -adrenergic agonist salbutamol^{32,89} has been reported to protect against ASA-induced attacks of asthma through a mechanism that seems unrelated to its bronchodilator properties. In a recently concluded study by Szczeklik et al,³² salmeterol effectively prevented bronchial reactions to inhalation of lysine-ASA in patients with AIA. It also attenuated the expected ASA-provoked rise in urinary excretion of LTE₄ and the stable PGD₂ metabolite. Thus salmeterol appears to directly interfere with eicosanoid metabolism in AIA, a finding which might be of clinical relevance.

Chronic eosinophilic rhinosinusitis frequently leads to the development of nasal polyps in patients with AIA. Treatment is difficult. Intranasal fluticasone is an effective treatment for rhinitis in many patients with AIA,⁹⁰ particularly when nasal passages are patent. LT modifiers provide benefit in many patients with AIA and also deserve a trial. Sinus/polyp operations are often performed, but recurrence of nasal polyps usually occurs. ASA desensitization followed by daily treatment with ASA 650 mg administered twice daily is also an option⁷⁰ and should be initiated when other measures fail or frequent sinus/polyp operations are required.

REFERENCES

1. Widal MF, Abrami P, Lenmoyez J. Anaphylaxie et idiosyncrasie. *Presse Med* 1922;30:189-92.
2. Samter M, Beers RF. Intolerance to aspirin. Clinical studies and consideration of its pathogenesis. *Ann Intern Med* 1968;68:975-83.
3. Drazen JM, Israel E, O'Byrne PM. Treatment of asthma with drugs modifying the leukotriene pathway. *N Engl J Med* 1999;340:197-206.
4. Nasser SMS, Lee TH. Leukotrienes in aspirin-sensitive asthma. In: Szczeklik A, Gryglewski RJ, Vane JR, editors. *Eicosanoids, aspirin and asthma*. New York: Marcel Dekker, Inc; 1998. p. 317-35.
5. Stevenson DD, Simon RA. Sensitivity to aspirin and nonsteroidal antiinflammatory drugs. In: Middleton E, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, Busse WW, editors. *Allergy: principles and practice*. 5th ed. St Louis: Mosby; 1998. p. 1225-34.
6. Quiralte J, Blanco C, Castillo R, Delgado J, Carrillo T. Intolerance to nonsteroidal antiinflammatory drugs: results of controlled drug challenges in 98 patients. *J Allergy Clin Immunol* 1996;98:678-85.
7. Szczeklik A. Mechanism of aspirin-induced asthma. In: Szczeklik A, Gryglewski RJ, Vane JR editors. *Eicosanoids, aspirin and asthma*. New York: Marcel Dekker, Inc; 1998. p. 299-315.
8. Szczeklik A, Sanak M. Genetics of aspirin-induced asthma. *Am J Respir Crit Care Med* In press.
9. Picado C, Castillo JA, Montserrat JM, Augusti-Vidal A. Aspirin intolerance as a precipitating factor of life-threatening attacks of asthma requiring mechanical ventilation. *Eur Respir J* 1989;2:127-9.
10. Marquette CH, Saulnier F, Leroy O, Wallaert B, Chopin C, Demarcq JM, et al. Long-term prognosis for near-fatal asthma. A 6-year follow-up study of 145 asthmatic patients who underwent mechanical ventilation for near-fatal attack of asthma. *Am Rev Respir Dis* 1992;146:76-81.
11. Bochenek G, Nizankowska E, Szczeklik A. Atopy trait in hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy* 1996;51:16-23.
12. Bianco S, Robuschi M, Pettrigni G. Aspirin-induced tolerance in aspirin-induced asthma detected by a new challenge technique. *Int Res Com Syst Med Sci* 1977;5:129-30.
13. Milewski M, Mastalerz L, Nizankowska E, Szczeklik A. Nasal provoca-

- tion test for diagnosis of aspirin-induced asthma. *J Allergy Clin Immunol* 1998;101:581-6.
14. Schlumberger HD. Drug-induced pseudo-allergic syndrome as exemplified by acetylsalicylic acid intolerance. In: Dukor P, Kallos P, Schlumberger HD, West GB, editors. *Pseudo-allergic reactions. Involvement of drugs and chemicals*. Basel: Karger; 1980. p. 125-203.
 15. Dahlen B, Boreus LO, Anderson P, Anderson R, Zetterstrom O. Plasma acetylsalicylic acid and salicylic acid levels during aspirin provocation in aspirin-sensitive subjects. *Allergy* 1994;49:43-9.
 16. Szczeklik A. The cyclooxygenase theory of aspirin-induced asthma. *Eur Respir J* 1990;3:588-93.
 17. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature* 1971;231:232-4.
 18. Szczeklik A, Gryglewski RJ, Czerniawska-Mysik G. Relationship of inhibition of prostaglandin biosynthesis by analgesics to asthma attacks in aspirin-sensitive patients. *BMJ* 1975;1:67-9.
 19. Szczeklik A, Gryglewski RJ, Czerniawska-Mysik G. Clinical patterns of hypersensitivity to nonsteroidal antiinflammatory drugs and their pathogenesis. *J Allergy Clin Immunol* 1977;60:276-84.
 20. Stevenson DD, Lewis RA. Proposed mechanisms of aspirin sensitivity reactions. *J Allergy Clin Immunol* 1987;80:788-90.
 21. Lee TH. Mechanism of aspirin sensitivity. *Am Rev Respir Dis* 1992;145:34-6.
 22. Demoly P, Jaffuel D, Lequeux N, Weksler B, Creminon Ch, Michel F-B, et al. Prostaglandin H synthase 1 and 2 immunoreactivities in the bronchial mucosa of asthmatics. *Am J Respir Crit Care Med* 1997;155:670-5.
 23. Sousa AR, Pfister R, Christie PE, Lane SJ, Nasser SM, Schmitz-Schumann M, et al. Enhanced expression of cyclo-oxygenase isoenzyme 2 (COX-2) in asthmatic airways and its cellular distribution in aspirin-sensitive asthma. *Thorax* 1997;52:940-5.
 24. Cowburn AS, Sladek K, Soja J, Adamek L, Nizankowska E, Szczeklik A, et al. Overexpression of leukotriene C4 synthase in bronchial biopsies from patients with aspirin-intolerant asthma. *J Clin Invest* 1998;101:1-13.
 25. Bianco S, Robuschi M, Petrigni G, Scuri M, Pietroni MG, Refini RM, et al. Efficacy and tolerability of nimesulide in asthmatic patients intolerant to aspirin. *Drugs* 1993;46:115-20.
 26. Kosnik M, Music E, Matjaz F, Suskovic S. Relative safety of meloxicam in NSAID-intolerant patients. *Allergy* 1998;53:1231-3.
 27. Hawkey CJ. COX-2 inhibitors. *Lancet* 1999;353:307-14.
 28. Szczeklik A, Sladek K, Dworski R, Nizankowska E, Soja J, Sheller J, et al. Bronchial aspirin challenge causes specific eicosanoid response in aspirin sensitive asthmatics. *Am J Respir Crit Care Med* 1996;154:1608-14.
 29. Fischer AR, Rosenberg MA, Lilly CM, Callery JC, Rubin P, Cohn J, et al. Direct evidence for a role of the mast cell in the nasal response to aspirin in aspirin-sensitive asthma. *J Allergy Clin Immunol* 1994;94:1046-56.
 30. Warren MS, Sloan SJ, Westcott JY, Hamilos D, Wenzel SE. LTE4 increases in bronchoalveolar lavage fluid (BALF) of aspirin-intolerant asthmatics (AIA) after instillation of indomethacin [abstract]. *J Allergy Clin Immunol* 1995;95:170.
 31. O'Sullivan S, Dahlen B, Dahlen S-E, Kumlin M. Increased urinary excretion of the prostaglandin D2 metabolite 9 α , 11 β -prostaglandin F2 after aspirin challenge supports mast cell activation in aspirin-induced airway obstruction. *J Allergy Clin Immunol* 1996;98:421-32.
 32. Szczeklik A, Dworski R, Mastalerz L, Prokop A, Sheller JR, Nizankowska E, et al. Salmeterol prevents aspirin-precipitated attacks of asthma and interferes with eicosanoids metabolism. *Am J Respir Crit Care Med* 1998;158:1168-72.
 33. Szczeklik A. Aspirin-induced asthma as a viral disease. *Clin Allergy* 1988;18:15-20.
 34. Pavord ID, Tattersfield AE. Bronchoprotective role for endogenous prostaglandin E2. *Lancet* 1995;345:436-8.
 35. Kuehl FA, Dougherty WH, Ham EA. Interactions between prostaglandins and leukotrienes. *Biochem Pharmacol* 1984;33:1-5.
 36. Christman BW, Christman JW, Dworski R, Blair IA, Prakash C. Prostaglandin E2 limits arachidonic acid availability and inhibits leukotriene B4 synthesis in rat alveolar macrophages by a nonphospholipase A2 mechanism. *J Immunol* 1993;151:2096-104.
 37. An S, Goetzel EJ. Lipid mediators of hypersensitivity and inflammation. In: Middleton E, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, Busse WW, editors. *Allergy: principles and practice*. 5th ed. St Louis: Mosby; 1998. p. 168-82.
 38. Kahn RM, Okanami DA, Jacoby DB, Fryer AD. Viral infection induced dependence of neuronal M2 muscarinic receptors on cyclooxygenase in guinea pig lungs. *J Clin Invest* 1996;98:299-307.
 39. Sestini P, Armetti L, Gambaro G, Pieroni MG, Refini RM, Sala A, et al. Inhaled PGE2 prevents aspirin-induced bronchoconstriction and urinary LTE4 excretion in aspirin-sensitive asthma. *Am J Respir Crit Care Med* 1996;153:572-5.
 40. Szmidi M, Wasiaik W. The influence of misoprostol (synthetic analogue of prostaglandin E1) on aspirin-induced bronchoconstriction in aspirin-sensitive asthma. *J Invest Allergol Clin Immunol* 1996;6:121-5.
 41. Smith CM, Hawksworth RJ, Thien FC, Christie PE, Lee TH. Urinary leukotriene E4 in bronchial asthma. *Eur Respir J* 1992;5:693-9.
 42. Kumlin M, Dahlen B, Bjorck T, Zetterstrom O, Granstrom E, Dahlen S-E. Urinary excretion of leukotriene E4 and 11-dehydro-thromboxane B2 in response to provocations with allergen, aspirin, leukotriene D4 and histamine in asthmatics. *Am Rev Respir Dis* 1992;146:96-103.
 43. Sladek K, Szczeklik A. Cysteinyl leukotrienes overproduction and mast cell activation in aspirin-provoked bronchospasm in asthma. *Eur Respir J* 1993;6:391-9.
 44. Ortolani C, Mironi C, Fontana A, Folco GC, Miadonna A, Montalbetti N, et al. Study of mediators of anaphylaxis in nasal wash fluids after aspirin and sodium metabisulfite nasal provocation in intolerant rhinitic patients. *Ann Allergy* 1987;59:106-12.
 45. Ferreri NR, Howland WC, Stevenson DD, Spiegelberg HL. Release of leukotrienes, prostaglandins and histamine into nasal secretions of aspirin-sensitive asthmatic during reaction to aspirin. *Am Rev Respir Dis* 1988;137:847-54.
 46. Picado C, Ramis I, Rosello J, Prat J, Bulbena O, Plaza V, et al. Release of peptido-leukotrienes into nasal secretions after local instillation of aspirin in aspirin-sensitive asthmatic patients. *Am Rev Respir Dis* 1992;145:65-9.
 47. Kowalski ML, Sliwiska-Kowalska M, Igarashi Y, White MV, Wojciechowska B, Brayton P, et al. Nasal secretions in response to acetylsalicylic acid. *J Allergy Clin Immunol* 1993;91:580-98.
 48. Mewes T, Riechelmann H, Klimek L. Increased in vitro cysteinyl leukotriene release from blood leukocytes in patients with asthma, nasal polyps, and aspirin intolerance. *Allergy* 1996;51:506-10.
 49. Penrose JF, Spector J, Baldasaro M, Xu K, Arm JP, Austen KF, et al. Molecular cloning for human LTC4 synthase: organization, nucleotide sequence and chromosomal localization to 5q35. *J Biol Chem* 1996;271:11356-61.
 50. Sanak M, Simon H-U, Szczeklik A. Leukotriene C4 synthase promoter polymorphism and risk of aspirin-induced asthma. *Lancet* 1997;350:1599-600.
 51. Sanak M, Bazan-Socha S, Szczeklik A. Leukotriene C4 synthase (LTC4s) expression in blood eosinophils of patients with asthma. *Eur Respir J* 1998;12(suppl 28):373s.
 52. Szczeklik A, Sanak M, Nizankowska E, Mastalerz L, Bochenek G, Pulka G, et al. Leukotriene C4 synthase genetic polymorphism directs urinary cysteinyl-leukotriene response to aspirin-challenge in asthma. *Allergy* 1998;53(suppl 43):61.
 53. Arm JP, O'Hickey SP, Spur B, Lee TH. Airway responsiveness to histamine and leukotriene E4 in subjects with aspirin-induced asthma. *Am Rev Respir Dis* 1989;140:148-53.
 54. Serhan CN. Lipoxins and novel aspirin-triggered 15-epi-lipoxins (ATL): A jungle of cell-cell interactions or a therapeutic opportunity? *Prostaglandins* 1997;53:107-37.
 55. In KH, Asano K, Beier D, Grobholz J, Finn PW, Silverman EK, et al. Naturally occurring mutation in the human 5-lipoxygenase gene promoter that modify transcription factor binding and reporter gene transcription. *J Clin Invest* 1997;99:1130-7.
 56. Nasser SMS, Pfister R, Christie PE, Sousa AR, Barker J, Schmitz-Schumann M, et al. Inflammatory cell populations in bronchial biopsies from aspirin-sensitive asthmatic subjects. *Am J Respir Crit Care Med* 1996;153:90-6.
 57. Hamilos DL, Leung DYM, Wood R, Bean DK, Song YL, Schotman E, et al. Eosinophil infiltration in nonallergic chronic hyperplastic sinusitis with nasal polyposis (CHSINP) is associated with endothelial VCAM-1 upregulation and expression of TNF- α . *Am J Respir Cell Mol Biol* 1996;15:443-50.

58. Sousa AR, Lams BEA, Pfister R, Christie PE, Schmitz M., Lee TH. Expression of interleukin-5 and granulocyte-macrophage colony-stimulating factor in aspirin-sensitive and non-aspirin-sensitive asthmatic airways. *Am J Respir Crit Care Med* 1997;156:1384-9.
59. Holgate ST, Bodey KS, Janezic A, Frew AJ, Kaplan AP, Teran LM. Release of Rantes, MIP-1 α , and MCP-1 into asthmatic airways following endobronchial allergen challenge. *Am J Respir Crit Care Med* 1997;156:1377-83.
60. Szczeklik A, Nizankowska E, Serafin A, Dyczek A, Duplaga M, Musial J. Autoimmune phenomena in bronchial asthma with special reference to aspirin intolerance. *Am J Respir Crit Care Med* 1995;152:1753-6.
61. Lasalle P, Delneste Y, Gosset P, Grass-Masse H, Wallaert B, Tonnel AB. T and B cell immune response to a 55-kDa endothelial cell-derived antigen in severe asthma. *Eur J Immunol* 1993;23:796-803.
62. Szczeklik A, Musial J, Pulka G. Autoimmune vasculitis and aortic stenosis in aspirin-induced asthma (AIA). *Allergy* 1997;52:352-4.
63. Szczeklik A, Schmitz-Schumann M, Nizankowska E, Milewski M, Roehlig F, Virchow C. Altered distribution of IgG subclasses in aspirin-induced asthma: high IgG4, low IgG1. *Clin Exp Allergy* 1992;22:283-7.
64. Dekker JW, Nizankowska E, Schmitz-Schumann M, Pile K, Bochenek G, Dyczek A, et al. Aspirin-induced asthma and HLA-DRB1 and HLA-DPB1 genotypes. *Clin Exp Allergy* 1997;27:574-7.
65. Nizankowska E, Duplaga M, Bochenek G, Szczeklik A, on behalf of the AIAE project. Clinical course of aspirin-induced asthma: results of AIAE. In: Szczeklik A, Gryglewski RJ, Vane JR, editors. *Eicosanoids, aspirin and asthma*. New York: Marcel Dekker, Inc; 1998. p. 451-71.
66. Nizankowska E, Soja J, Pinis G, Bochenek G, Sladek K, Domagala B, et al. Treatment of steroid-dependent bronchial asthma with cyclosporin. *Eur Respir J* 1995;8:1091-9.
67. Settiple RA, Shrank PJ, Simon RA, Mathison DA, Christensen SC, Stevenson DD. Prevalence of cross-sensitivity with acetaminophen in aspirin-sensitive asthmatics. *J Allergy Clin Immunol* 1995;96:480-5.
68. Andri L, Senna G, Betteli C, Giovanni S, Scaricabarozzi I, Mezzelani P, et al. Tolerability of nimesulide in aspirin-sensitive patients. *Ann Allergy* 1994;72:29-32.
69. Kowalski ML. Management of aspirin-sensitive rhinosinusitis-asthma syndrome: What role for aspirin desensitization? *Allergy Proc* 1992;13:175-84.
70. Stevenson DD, Hankammer MA, Mathison DA, Christiansen SC, Simon RA. Aspirin desensitization/treatment of aspirin-sensitive rhinosinusitis-asthmatic patients: long term outcomes. *J Allergy Clin Immunol* 1996;98:751-8.
71. Juergens UR, Christiansen SC, Stevenson DD, Zuraw BL. Inhibition of monocyte leukotriene B4 production after aspirin desensitization. *J Allergy Clin Immunol* 1995;96:148-56.
72. Nasser S, Patel M, Bell GS, Lee TH. The effect of aspirin desensitization on urinary leukotriene E4 concentrations in aspirin-sensitive asthma. *Am J Respir Crit Care Med* 1995;151:1326-30.
73. Szczeklik A, Nizankowska E, Czerniawska-Mysik G, Sek S. Hydrocortisone and airflow impairment in aspirin-induced asthma. *J Allergy Clin Immunol* 1985;76:530.
74. Feigenbaum BA, Stevenson DD, Simon RA. Hydrocortisone sodium succinate does not cross-react with aspirin in aspirin-sensitive patients with asthma. *J Allergy Clin Immunol* 1995;96:545-8.
75. Weber RW, Hoffman M, Raine DA, Nelson HS. Incidence of bronchoconstriction due to aspirin, azo dyes, non-azo dyes and preservatives in a population of perennial asthmatics. *J Allergy Clin Immunol* 1979;64:32-7.
76. Stevenson DD, Simon RA, Lumry WR, Mathison DA. Adverse reactions to tartrazine. *J Allergy Clin Immunol* 1986;78:182-91.
77. Virchow C, Szczeklik A, Bianco S, Schmitz-Schumann M, Juhl E, Robuschi M, et al. Intolerance to tartrazine in aspirin-induced asthma: result of a multicenter study. *Respiration* 1988;53:20-5.
78. Gerber JG, Payne NA, Oelz O, Nies AS, Oates JA. Tartrazine and the prostaglandin system. *J Allergy Clin Immunol* 1979;63:289-94.
79. Christie PE, Smith CM, Lee TH. The potent and selective sulfidopeptide leukotriene antagonist SK&F 104353, inhibits aspirin-induced asthma. *Am Rev Respir Dis* 1991;144:957-8.
80. Yamamoto H, Nagata M, Kuramitsu K, Tabe K, Kiuchi H, Sakamoto Y, et al. Inhibition of analgesic-induced asthma by leukotriene receptor antagonist ONJ-VC 1078. *Am J Respir Crit Care Med* 1994;150:254-7.
81. Nasser SMS, Bell GS, Foster S, Spruce KE, Macvillan R, Williams AJ, et al. Effect of the 5-lipoxygenase inhibitor ZD 2138 on aspirin-induced asthma. *Thorax* 1994;49:749-56.
82. Israel E, Fisher AR, Rosenberg MA, Lilly CM, Callery JC, Hapero J, et al. The pivotal role of 5-lipoxygenase products in the reaction of aspirin-sensitive asthmatics to aspirin. *Am Rev Respir Dis* 1993;148:1447-51.
83. Pauls JD, Simon RA, Daffern P, Stevenson DD. Effectiveness of the 5-LO inhibitor zileuton during oral challenges in aspirin-sensitive asthmatics. *J Allergy Clin Immunol* 1999;103:S229.
84. Dahlen B, Nizankowska E, Szczeklik A, Zetterström O, Bochenek G, Kumlin M, et al. Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. *Am J Respir Crit Care Med* 1998;157:1187-94.
85. Kuna P, Malmstrom K, Dahlen S-E, Nizankowska E, Kowalski M, Stevenson D, et al. Montelukast (MK-0476) a CysLT1 receptor antagonist improves asthma control in aspirin-intolerant asthmatic patients [abstract]. *Am J Respir Crit Care Med* 1997;155:A975.
86. Wechsler ME, Garpestad E, Flier SR, Kocher O, Weiland DA, Polito AJ, et al. Pulmonary infiltrates, eosinophilia and cardiomyopathy following corticosteroid withdrawal in patients with asthma receiving zafirlukast. *JAMA* 1998;279:455-7.
87. Churg A, Churg J. Steroids and the Churg-Strauss syndrome. *Lancet* 1998;352:32.
88. Green RL, Vayonis AG. Churg-Strauss syndrome after zafirlukast in two patients not receiving systemic steroid treatment. *Lancet* 1999;353:725-6.
89. Szczeklik A, Mastalerz L, Nizankowska E, Cmiel A. Protective and bronchodilator effects of prostaglandin E and salbutamol in aspirin-induced asthma. *Am J Respir Crit Care Med* 1996;153:567-71.
90. Mastalerz L, Milewski M, Duplaga M, Nizankowska E, Szczeklik A. Intranasal fluticasone propionate for chronic eosinophilic rhinitis in patients with aspirin-induced asthma. *Allergy* 1997;52:895-900.