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Aspirin-Induced Asthma
Clinical Aspects, Pathogenesis and Management

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Abstract

Aspirin (acetylsalicylic acid)-induced asthma (AIA) consists of the clinical triad of asthma, chronic rhinosinusitis with nasal polyps, and precipitation of asthma and rhinitis attacks in response to aspirin and other NSAIDs. The prevalence of the syndrome in the adult asthmatic populations is approximately 4–10%. Respiratory disease in these patients may be aggressive and refractory to treatment.

The aetiology of AIA is complex and not fully understood, but most evidence points towards an abnormality of arachidonic acid (AA) metabolism. Cyclooxygenase (COX), the rate-limiting enzyme in AA metabolism, exists as two main isoforms. COX-1 is the constitutive enzyme responsible for synthesis of protective prostanoids, whereas COX-2 is induced under inflammatory conditions. A number of theories regarding its pathogenesis have been proposed. The shunting hypothesis proposes that inhibition of COX-1 shunts AA metabolism away from production of protective prostanoids and towards cysteinyl leukotriene (cys-LT) biosynthesis, resulting in bronchoconstriction and increased mucus production. The COX-2 hypothesis proposes that aspirin causes a structural change in COX-2 that results in the generation of products of the lipoxygenase pathway. It is speculated that this may result in the formation of mediators that cause respiratory reactions in AIA.

Related studies provide evidence for abnormal regulation of the lipoxygenase pathway, demonstrating elevated levels of cys-LTs in urine, sputum and peripheral blood, before and following aspirin challenge in AIA patients. These studies suggest that cys-LTs are continually and aggressively synthesised before exposure to aspirin and, during aspirin-induced reactions, acceleration of synthesis occurs. A genetic polymorphism of the *LTC4S* gene has been identified consisting of an A to C transversion 444 nucleotides upstream of the first codon, conferring a relative risk of AIA of 3.89. Furthermore, carriers of the C444 allele demonstrate a dramatic rise in urinary LTE_4 following aspirin provocation, and respond better to the cys-LT antagonist pranlukast than A444 homozygotes.

AIA patients have an aggressive form of disease, and treatment should include combination therapy with inhaled corticosteroids, β_2-adrenoceptor agonists and LT modifiers. Furthermore, recently developed inhibitors of COX-2 may be safer in patients with AIA.

Since the discovery of aspirin (acetylsalicylic acid) about a century ago, many NSAIDs have been used for the treatment of inflammatory states and pain. While the NSAIDs are generally well tolerated and effective, common adverse effects frequently limit therapy. This is particularly notable in the respiratory tract where a subset of patients with asthma develop an aggressive mucosal inflammatory disease within hours of ingesting aspirin and most other NSAIDs. Aspirin-induced asthma (AIA) forms part of a syndrome that includes rhinitis and nasal polyposis. The recent introduction of leukotriene (LT)-modifying drugs has amplified interest in this syndrome. In this article we discuss advances in the pathogenesis and management of AIA, starting with a brief presentation of its clinical features.

1. Clinical Features

The triad of aspirin intolerance, sinusitis with nasal polyposis and asthma, 'Samter's syndrome', was first described by Samter and Beers.[1] The syndrome, now more commonly called AIA or aspirin-exacerbated respiratory disease, is a clinical syndrome characterised by chronic rhinosinusitis, nasal polyposis, asthma, and precipitation of asthma and rhinitis attacks after ingestion of aspirin and most other NSAIDs.[2] Although precipitation of asthma attacks by ingestion of aspirin and other NSAIDs is considered a hallmark of the syndrome, the respiratory mucosal inflammatory disease process begins and continues in the absence of ongoing or even intermittent exposure to aspirin or NSAIDs. The disease develops in a characteristic way that might suggest a common underlying mechanism. The typical patient with AIA is an adult (more common in women than men) who develops refractory chronic rhinitis in the third or fourth decade of life, often after a viral respiratory illness. The chronic rhinitis evolves into chronic eosinophilic rhinosinusitis with associated nasal polyposis that results in anosmia in most patients. Computed tomography of the sinuses most often demonstrates pansinusitis and patients often undergo multiple sinus operations resulting in only limited temporary benefit. During the evolution of the sinus disease persistent asthma develops. Finally, if patients are exposed to aspirin or NSAIDs, acute respiratory reactions begin to occur.

Despite subsequent avoidance of aspirin and other NSAIDs, the respiratory mucosal inflammatory disease persists, often requiring systemic corticosteroids for control of both upper and lower respiratory tract symptoms. Adequate control of asthma can often only be accomplished with the simultaneous control of the associated rhinosinusitis. With few exceptions, once AIA develops it remains for the rest of the patient's life.[2]

Estimates of AIA prevalence in adults with asthma range from 4.3%[3] to 10.9%[4] in some populations, and it is possible that many patients are diag-

nosed who did not realise that aspirin made their asthma worse.[4] Our own anecdotal experience in Nottingham, UK, of trying to identify asthmatic patients by oral challenge suggests that these patients are rather more difficult to find than one might expect, based on the prevalence figures from questionnaire studies. Interestingly, in a study by Vally et al.[4] a number of individuals in the random cohort without a physician diagnosis of asthma reported respiratory symptoms in response to aspirin and other NSAIDs, suggesting that some persons with AIA may not be diagnosed with asthma.

1.1 Diagnosis

Although clinical history might raise the suspicion of AIA, it has been suggested that the gold standard for diagnosing AIA should be either oral or inhaled challenge with aspirin.[5] Nasal provocation test with aspirin has a high sensitivity and specificity in the diagnosis of AIA.[6-8] In the US, nasal provocation tests are unavailable and the diagnosis is made through graded aspirin challenge. Currently, nasal provocation tests rely on anterior rhinomanometry and clinical criteria to assess response. Rhinomanometry relies on airflow and, therefore, cannot be relied upon when there is significant nasal obstruction, which is common in the presence of rhinosinusitis and nasal polyps. Acoustic rhinometry may circumvent this problem, and may be of diagnostic use in the future.[8] An oral provocation test can be performed to confirm the result if the clinical situation of the patient permits it. Although aspirin provocation tests with improved diagnostic accuracy have been developed, no *in vitro* test has been found to be of diagnostic value.[5] At the biochemical level, AIA is characterised by a long-term overproduction of cysteinyl LTs (cys-LTs).

2. Pathogenesis

A number of mechanisms have been proposed to explain the pathogenesis of AIA. Most evidence suggests that it is related to inhibition of synthesis of protective prostaglandins (PGs) by cyclo-oxygenase (COX), causing an imbalance of proinflammatory LTs. However, other possible mechanisms are also briefly considered in the following sections.

2.1 Allergic Mechanism

Clinical symptoms precipitated by aspirin 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 aspirin-lysine have been negative, and numerous attempts to demonstrate specific antibodies against aspirin or its derivatives were unsuccessful.[9] Furthermore, in patients with AIA, asthmatic attacks can be precipitated not only by aspirin but also by other NSAIDs with distinct chemical structures, frequently on first exposure to the new NSAID. All of these facts make immunological cross-reactivity most unlikely.

2.2 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.[10,11] In bronchial biopsy specimens of patients with AIA, eosinophils are 4-fold more numerous than in patients with aspirin-tolerant asthma (ATA) and 15-fold more numerous than in biopsy specimens of normal mucosa.[12] 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. Eosinophil infiltration of airway tissue appears to be a central feature of AIA. Eosinophil cationic protein (ECP) is found in bronchoalveolar lavage (BAL) fluid and increases after aspirin-lysine segmental challenge in patients with AIA.[13] Overexpression of interleukin (IL)-5 (known to be involved in the recruitment, activation, maturation and perpetuation of survival of eosinophils) is reported in the airways of patients with AIA.[14] Immunohistochemical staining of bronchial biopsy specimens shows that eosinophils are the predominant cells containing LTC_4 synthase, the essential enzyme for cys-LT synthesis.[15] Thus, sheer numbers of eosinophils, loaded with normally

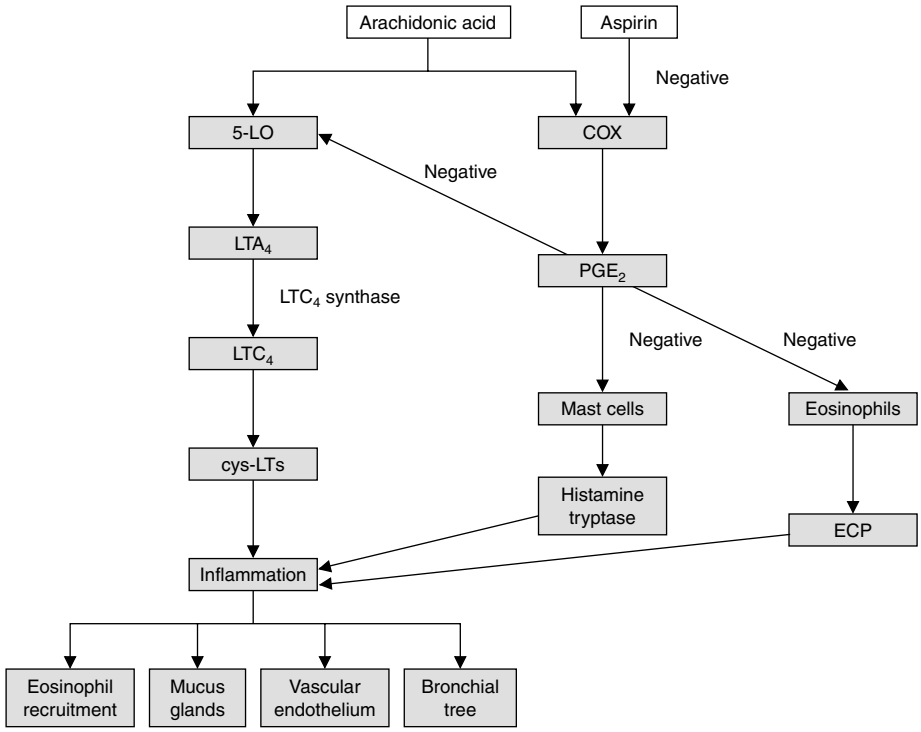

Fig. 1. Possible mechanisms of airway inflammation in aspirin (acetylsalicylic acid)-induced asthma. Aspirin inhibits cyclo-oxygenases (COXs) with resulting block of protective prostanoids, mainly prostaglandin E_2 (PGE_2). PGE_2 normally inhibits degranulation of mast cells and release of eosinophil cationic protein (ECP) from eosinophils. It also suppresses 5-lipoxygenase (5-LO) activity leading to a balance between the anti-inflammatory PGE_2 and proinflammatory cysteinyl leukotrienes (cys-LTs). The end results will be excessive formation of cys-LTs.

expressed or increased cys-LT enzymes, may be responsible for overproduction of total cys-LTs, a differentiating feature of AIA (see sections 2.3.1 and 2.4).

Persistent airway inflammation in AIA could result from non-IgE-mediated reactions to an endogenous antigen or virus.[16] These possibilities are supported by the finding of elevated markers of autoimmunity,[17-19] enhanced IgG_4 synthesis,[20] and human leucocyte antigen association with AIA.[17-19] A latent virus infection could:[21] (i) modify the genetic message for COX molecules, altering response to NSAIDs by synthesising unknown metabolites that stimulate cys-LT production; (ii) evoke an immunological response, perhaps dominated by specific cytotoxic lymphocytes and eosinophils, previously suppressed by PGE_2; or (iii) leave DNA fragments in native DNA, which might direct synthesis of altered enzymes.

2.3 The Cyclo-oxygenase (COX) Pathway

COX is the rate-limiting enzyme in the formation of prostanoids from arachidonic acid (AA). A summary of AA metabolism and effects of its metabolites on airway inflammation is shown in figure 1. There are three isoforms of COX, namely COX-1, COX-2 and the newly identified COX-3.[22] COX-1 is the housekeeping enzyme, responsible for physiological activities of PGs, while COX-2, the expression of which is induced under inflammatory conditions, is responsible for pathological PGs that produce pain and fever.[23] COX-3 is a spliced COX-1 variant with unknown function.[24] PG production consists of several stages. The conversion of membrane phospholipid to AA via phospholipase A_2 is

followed by the subsequent conversion of AA to PGH_2 by COX.[25] This is a two-step process involving COX activity to convert AA to PGG_2 and a peroxidase reaction to produce PGH_2. Thereafter, PGH_2 can be converted to thromboxanes or to PGs (PGD_2, $PGF_{2\alpha}$, PGE_2 and PGI_2) by specific synthases or isomerases. The COX metabolites released from a particular cell are cell specific, reflecting the isomerase and synthase complement of that cell. These isomerases and synthases are, therefore, important in determining whether a cell produces mainly protective or proinflammatory prostanoids. It has been recognised for a long time that airway inflammatory cells produce proinflammatory prostanoids such as PGD_2 and $PGF_{2\alpha}$[26] and that airway structural cells, including epithelial cells and smooth muscle cells, produce protective PGs such as PGE_2.[27-29] Prostanoids have a number of potent effects on airway function in asthma. They can be subdivided into stimulatory PGs, such as PGD_2, $PGF_{2\alpha}$ and thromboxanes, and inhibitory PGs such as PGE_2.[30] PGE_2 has profound regulatory effects on other inflammatory systems: (i) it reduces cys-LT biosynthesis through inhibition of 5-lipoxygenase;[31-33] (ii) it inhibits cholinergic transmission, which can be deregulated by chronic viral infection;[34] (iii) it prevents discharge of granular mediators from mast cells;[33] and (iv) it prevents aspirin-precipitated bronchoconstriction and the expected rise in urinary LTE_4 when given by means of inhalation to patients with AIA[35] or as an oral PGE_2 analogue (misoprostol).[36]

Szczeklik et al.[37,38] were the first to propose a link between the ability of certain anti-inflammatory drugs to inhibit PG biosynthesis and precipitation of asthma attacks in aspirin-sensitive patients,[37] and went on to formulate the COX theory of AIA.[38]

2.3.1 The Shunting Hypothesis

Aspirin-induced bronchoconstriction is thought to be caused by shunting of AA metabolism away from prostanoid production into LT biosynthesis causing an increase in LT production and resultant bronchoconstriction and increased mucus production.[39] Consistent with this 'shunting hypothesis' the dose response curve to aspirin can be shifted by LT antagonists.[40,41]

Considering the protective effects of exogenous PGE_2 on aspirin-induced bronchoconstriction and the interdependence of PGE_2 and cys-LT production, reduced PGE_2 synthesis may render aspirin-sensitive patients more susceptible to the inhibitory effect of NSAIDs and also lead to an increase in cys-LT release. This hypothesis is supported by several studies that have shown a relative excess of proinflammatory eicosanoids in aspirin-sensitive patients. Kowalski et al.[42] studied cultured nasal epithelial cells from patients with aspirin-sensitive asthma with nasal polyps and rhinosinusitis (ASARS) and aspirin-tolerant controls with nasal polyps and rhinosinusitis (ATRS).[42] Basal PGE_2 levels in the ASARS group were significantly lower than in the ATRS group and basal levels of 15-hydroxyeicosatetraenoic acid (15-HETE, a proinflammatory eicosanoid produced from AA by the action of 15-lipoxygenase) were similar in both groups. Incubation with aspirin caused a similar relative inhibition of PGE_2 release in both groups, but 15-HETE production was enhanced in the ASARS group only, producing a relative excess of 15-HETE in this group. Sanek et al.[43] studied whole blood from AIA and ATA patients. Basal levels of pro-inflammatory LTC_4 were equal in both groups, whereas levels of lipoxin A_4 (LXA_4) and 15-epi-LXA_4, (inhibitors of inflammation and bronchoconstriction) were higher in ATA. In the presence of aspirin, ATA samples generated significantly more 15-epi-LXA_4, whereas AIA samples did not. Schäfer et al.[44] looked at eicosanoid levels in peripheral blood after bronchial provocation with lysine-aspirin in AIA patients, ATA patients and healthy controls. They also found basal PGE_2 levels markedly reduced in AIA, and peptidyl-LTs (pLTs) elevated. In AIA, following aspirin challenge, PGE_2 levels were unchanged and pLTs were massively increased, resulting in a relative excess of proinflammatory mediators in the AIA group.

Immunostaining techniques have shown that the overall expression of COX-1 and COX-2 is similar in bronchial biopsy specimens obtained from AIA

and ATA patients.[12,45] Furthermore, after bronchial challenge with aspirin-lysine, cells in BAL fluid staining for COX-1 or COX-2 were not found to be increased preferentially in patients with AIA.[12] Recent studies have reported that patients with AIA have decreased activity of COX-2 and lower production of PGE_2 in the upper airway and peripheral blood cells.[39,46] Picado et al.[47] found that COX-2 messenger RNA (mRNA) expression was reduced in nasal polyps from AIA patients compared with ATA patients and healthy controls, whilst there was no difference in COX-1 mRNA expression.[47] The investigators hypothesise that the drastically reduced amount of COX-2 results in chronically reduced levels of protective PGE_2, thereby leaving these patients susceptible to the effects of aspirin.

As mentioned in section 2.3, COX-1 is the housekeeping enzyme that is predominantly involved in the production of protective prostanoids. Thus, it has been thought that COX-1 inhibition is the cause of aspirin-induced reactions in aspirin-sensitive patients.[48] Evidence supporting this can be found in reports demonstrating that other salicylates, which are devoid of effect on COX-1 in intact cells, are well tolerated by patients with AIA.[49] More recently, highly selective inhibitors of COX-2 have been introduced into clinical practice. Theoretically, these should not cross-react with aspirin because of the preservation of constitutive PGE_2 synthesis. A number of studies have now shown that these drugs can be safely administered to patients with AIA, although caution should still probably be advised.[50-52] After aspirin desensitisation, cross-desensitisation to other NSAIDs that inhibit COX also occurs.[53] These data support the evidence for the role of inhibition of COX-1 in AIA.

Activated mast cells are a likely source of proinflammatory PGs in addition to other mediators such as histamine and tryptase. A significantly higher concentration of PGD_2 (indicative of mast cell activation) in sputum from patients with AIA was found, suggesting possible ongoing mast cell activation in the lower airways.[54] When segmental bronchial challenges with aspirin were performed in patients with AIA and ATA, and COX products were measured in BAL fluid 15 minutes after installation of aspirin-lysine,[13] aspirin significantly depressed formation of PGE_2 and thromboxane B_2 in both groups; however, mean levels of PGD_2, $PGF_{2\alpha}$, and $9\alpha,11\beta$-PGF_2 (a stable PGD_2 metabolite) were not depressed in BAL fluid from patients with AIA, but were significantly decreased only in the control (ATA) patients. Fischer et al.[55] have investigated the role of mast cells in the pathogenesis of AIA. Following aspirin challenge in aspirin-sensitive patients, they found increased nasal tryptase, histamine and cys-LTs in nasal lavage fluid, suggestive of mast cell activation. A modest increase was seen in urinary levels of $9\alpha,11\beta$-PGF_2 in patients with AIA after aspirin-lysine bronchoprovocation challenges.[56] Intravenous aspirin provocation significantly increased urinary excretion of $9\alpha,11\beta$-PGF_2, and histamine in AIA patients compared with patients with ATA.[57] Finally, in stable AIA, though not in ATA, there is a steady release of PGD_2 into the blood, accompanied by the release of tryptase.[58] Aspirin enhances this reaction in most patients and the release of bronchoconstrictive PGD_2 might contribute to the severe clinical course of AIA.

Many studies have looked at the effects of COX inhibitors on bronchoconstrictor challenges in patients with ATA. The results of these studies are conflicting and depend on the inhibitor used, the route of administration and the type of patient studied. Indometacin can inhibit refractoriness and the bronchoprotective effect of inhaled furosemide (frusemide),[59] suggesting that under circumstances where protective PGs such as PGE_2 are produced these drugs have a deleterious effect. This effect contrasts with the effects during induced bronchoconstriction where the balance of prostanoid production has presumably shifted to proinflammatory prostanoids. Oral aspirin protected against the effects of ultrasonically nebulised distilled water in one study,[60] and oral indometacin had some effect on adenosine,[61] oxygen saturation[62] and antigen[63] challenge but responses to other challenges have been inconsistent. Flurbiprofen has a more consistent response when given orally, inhibiting

allergen-,[64] sodium metabisulphite-[65] and adenosine-induced[66] bronchoconstriction. The effect of inhaled COX inhibitors shows a more consistent protective effect. When given by inhalation both aspirin and indometacin protected against indirect bronchoconstrictor challenges with adenosine,[67] sodium metabisulphite[67] and allergen,[68] suggesting that the effect is class specific and is due to COX inhibition. In keeping with this, sodium salicylate was less effective.[67] How might one resolve these differences? The effect of COX inhibition will depend on the balance between the production of protective PGs such as PGE_2 by the airways and constrictor products such as PGD_2, $PGF_{2\alpha}$ and thromboxane A_2 from inflammatory cells under different circumstances. If the net effect were a reduction in protective PGs then COX inhibitors would be expected to have a detrimental effect. In contrast, a net reduction in proinflammatory PGs would be beneficial.

2.3.2 The COX-2 Hypothesis

Patients with AIA appear to have an increased number of COX-2-expressing mast cells.[45] It is hypothesised that COX-2 predominates in those patients and is modified biochemically by aspirin, blocking the normal prostanoid profile and facilitating the production of 5-lipoxygenase products.[69] This hypothesis is supported by evidence showing that aspirin can cause a structural change in COX-2 resulting in production of 15-HETE (normally a 15-lipoxygenase metabolite).[69] Consequently, in patients where COX-2 predominates AA is still utilised by COX and the metabolites merely diverted. In various airway cells induced to express COX-2, the normal conversion of AA to PGE_2 is blocked by aspirin[70] and 15-HETE is formed.[71] It has been shown that endothelial cells treated to express COX-2 produced 15-HETE in the presence of aspirin which, in turn, was metabolised by 15-lipoxygenase in associated neutrophils forming a group of metabolites known as the 15-epilipoxins.[72] However, the functional consequences of the production of these compounds remain unknown. It is speculated that this putative pathway for the generation of 5-lipoxygenase products may result in the formation of mediators that cross react with known cys-LTs and account for the observed effects in AIA.[69] This is supported by clinical observations that cys-LT receptor antagonists attenuate aspirin-induced bronchoconstriction,[73] although the effect of the 5-lipoxygenase inhibitor zileuton can be overcome by escalating doses of aspirin.[74]

Thus, disruption of synthesis of some prostanoids (PGE_2 and PGI_2) and/or diversionary synthesis of others after interactions between aspirin and COX enzymes seem to be crucial events in the pathogenesis of AIA. Why the interruption of PGE_2 synthesis by aspirin does not induce respiratory reactions in all humans, or at least all asthmatic patients, is not completely understood. It may be that, due to the overproduction of cys-LTs in AIA patients, the sudden drop in PGE_2 and consequent loss of the anti-inflammatory effect of PGE_2 following ingestion of aspirin results in profound bronchoconstriction. Non-aspirin-sensitive patients do not have the same degree of overproduction of LTs; hence, a sudden drop in PGE_2 would be unlikely to cause symptoms.

2.4 The Lipoxygenase Pathway

Cys-LTs are mediators released in asthma and are both direct bronchoconstrictors and proinflammatory substances that mediate several steps in the pathophysiology of chronic asthma, including inflammatory cell recruitment, vascular leakage and, possibly, airway remodelling. Most patients with AIA excrete 2- to 10-fold higher amounts of LTE_4 in urine than patients with ATA. The concentration of urinary LTE_4 was significantly higher in patients with AIA than in those with ATA and there was a significant correlation among the concentration of cys-LTs, the number of eosinophils and the concentration of eosinophil-derived neurotoxin in sputum.[54,57] Aspirin-induced immediate asthmatic reaction (IAR) in patients with AIA was associated with a fall in urinary thromboxane B_2, increased levels of sputum LTC_4, LTD_4 and ECP and urinary LTE_4.[40] The levels of sputum LTC_4, LTD_4 and urinary LTE_4 in the stable phase were significantly greater in AIA than ATA patients.[40]

Cys-LTs and 8-isoprostanes (a marker of oxidative stress) are also elevated in expired breath condensate of corticosteroid-naive patients with AIA, whereas cys-LTs are decreased in corticosteroid-treated patients.[75] Cys-LTs are also released into nasal secretions after oral or nasal challenge with aspirin-lysine.[13] This is accompanied by simultaneous inhibition of thromboxane B_2 and PGE_2, whereas 15-lipoxygenase metabolites remain unaltered.[76] Peripheral leucocytes obtained from patients with AIA showed greater cys-LT release on increasing aspirin exposure and flow cytometric analysis showed less eosinophil apoptosis when compared with normal leucocytes.[77] This increase in cys-LT release from blood leucocytes following aspirin stimulation seems to be unique to AIA and was not present in patients with ATA and in healthy controls.[78] Furthermore, the increase in cys-LT release from aspirin-stimulated peripheral blood leucocytes was inhibited by co-incubation with PGE_2.[78] These studies suggest that cys-LTs are continuously and aggressively synthesised in patients with AIA before any exposure to aspirin, and during aspirin-induced reactions marked acceleration of synthesis occurs. Thus, patients with AIA differ from other asthmatic and healthy subjects with respect to baseline levels of cys-LTs. Because synthesis of cys-LTs is already underway, release of the braking effect of PGE_2 caused by COX inhibition correlates with augmented cys-LT synthesis during aspirin-induced reactions.

The terminal enzyme for cys-LT production is LTC_4 synthase, the gene of which has been localised to chromosome 5q, telomeric to other candidate asthma genes, including IL-3, IL-4, IL-5 and granulocyte-macrophage colony-stimulating factor.[79] The expression of LTC_4 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 healthy control subjects. By contrast, expression of other LT pathways proteins (5-lipoxygenase, 5-lipoxygenase activating protein and LTA_4 hydrolase) was similar in all subject groups.[12] Increased LTC_4 synthase expression in biopsy specimens from patients with AIA was the only enzyme or cell marker that correlated significantly with bronchial hyperresponsiveness to inhaled aspirin-lysine,[12] a definitive clinical measure of AIA.

If cys-LTs are common mediators of bronchoconstriction in all asthmatic patients and mucosal inflammation in allergic rhinitis, why is there only a subset of patients who are aspirin sensitive? The answer eludes us, but certain possibilities have begun to emerge. As indicated earlier in section 2.3 and figure 1, the protective effects of PGE_2 in downregulating mast cells and 5-lipoxygenase are important in the ultimate synthesis of cys-LTs after aspirin interrupts synthesis of prostanoids. Furthermore, it was reported that thromboxane A_2 inhibits LTC_4 synthase activity in human platelets; indeed, a recent study by Tornhamre et al.[80] showed that oral aspirin administration can lead to uncoupling of thromboxane A_2-dependent negative feedback inhibition of LTC_4 synthase (although no differences were found between patients with AIA, ATA and healthy controls).

2.5 Genetic Polymorphism of Leukotriene C4 Synthase

Increased availability of the LTC_4 synthase enzyme may be achieved by genetic upregulation. The promoter region of the enzyme is complex and predicts interaction with many transcription enhancers. LTC_4 synthase is present in eosinophils and mast cells. Expression of LTC_4 synthase is variable, even in the same cell line. There is a polymorphism in the promoter region of the *LTC4S* gene, consisting of an A to C transversion, 444 nucleotides upstream of the first codon.[81] The C444 allele is more common in AIA patients compared with ATA or healthy controls. The relative risk of AIA associated with the C444 allele is 3.89. The transversion creates an additional core motif (CCCG) for transcription factor AP2 in the *cis* position, and it is proposed that the C444 polymorphism in the LTC_4 synthase promoter represents a risk factor for adverse reactions to NSAIDs in asthma by enhanced inducibility of the enzyme. Patients with AIA have upregulated LTC_4 synthase mRNA expression in

blood eosinophils, and increased gene transcripts are most pronounced in carriers of the C444 allele.[15] Although there is no relationship between *LTC4S* polymorphism and urinary LTE_4 excretion at baseline, provocation with aspirin leads to a dramatic increase in urinary LTE_4 in carriers of the C444 allele.[82] Interestingly, in a Japanese population with moderate asthma, C444 allele carriers responded better to the cys-LT antagonist pranlukast than A444 allele homozygotes.[83] Multivariate analysis suggested that the C444 genotype was an independent predictor of the clinical response to pranlukast.

Genetic studies have shown that individuals with a polymorphism in *LTC4S* that causes them to produce larger quantities of cys-LTs are more prone to developing AIA.[84,85] However, almost 30% of patients with AIA do not have a predisposing variant of the *LTC4S* gene, whereas 25% of the 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. A recent study looking at the frequency of this polymorphism in a Japanese population and its association with clinical characteristics[86] reported that the frequency of the C444 allele was significantly higher in patients with AIA than in patients with ATA. Variant C-allelic carriers experienced asthma at a significantly younger age than wild-type A homozygotes. Basal levels of LTE_4 and the increment of urinary LTE_4 on venous aspirin challenge did not show a difference between wild-type A homozygotes and variant C-allelic carriers. There was no relationship between the polymorphism and the LTC_4 synthase activity in eosinophils, although LTC_4 synthase activities were significantly higher in patients with AIA than in patients with ATA. These findings would be consistent with a multifactorial, polygenic aetiology of AIA, suggesting that the *LTC4S* polymorphism is only a partial explanation. 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, over-expression of LTC_4 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 signalling, like cys-LT receptors, play a significant role.[87] Enhanced responsiveness of cys-LT receptors to inhaled LTE_4 has been identified in patients with AIA,[87] and this phenomenon augments the effects of synthesised cys-LTs. Immunohistochemical staining of nasal mucosal biopsy specimens from patients with AIA and ATA showed increased expression of cys-LT receptors on inflammatory leucocytes in AIA patients with chronic rhinosinusitis and there was a downregulation of receptor expression after desensitisation to aspirin.[88] LXs are novel anti-inflammatory lipid mediators that also appear to facilitate the resolution of acute inflammatory responses.[89] These lipids are generated within the vascular lumen during multicellular responses, such as inflammation, and asthma. The mechanism of action of aspirin involves the triggering of carbon 15 epimers of LXs or 15-epilipoxins that mimic the bioactions of native LX.[89,90]

2.6 Diffuse Neuroendocrine System Pathology

One study found that AIA patients have a lower melatonin production in the daytime, a pathology of the platelet membrane-receptor complex and a pathological response to exogenous melatonin and aspirin.[91] The investigator hypothesises that AIA is an apudopathy caused by dysfunction of melatonin-producing cells. The reduced melatonin levels lead to reduced inhibitory action of melatonin on 5-lipoxygenase and nitric oxide synthase, and to enhanced platelet aggregation and activation, with a consequent increase in LTs. Furthermore, the study proposes that the reduced melatonin levels increase the sensitivity of platelets to aspirin, such that even minimal aspirin doses inhibit COX-1, shunting the already abnormal metabolism of AA and increasing LTs further. A new pathogenetic approach is pro-

posed to the treatment of AIA patients by correcting melatonin levels with peptide bioregulators – the epiphysis extracts epithalamin and epifamine. However, these data have not been reproduced or confirmed by other investigators. In support of these findings, one small study found that epifamine improved AIA patients' clinical condition.[92] Again, to our knowledge, this is the only study to demonstrate this.

3. Treatment

The general rules concerning treatment of AIA do not differ from the published guidelines on the management of asthma, reviewed by Tattersfield et al.[93] As mentioned in section 1, despite avoidance of aspirin and other NSAIDs, the respiratory mucosal inflammatory disease persists and often requires corticosteroids for control of both upper and lower respiratory tract symptoms. Inhaled corticosteroids (ICS) are now considered as first-line therapy in all asthma treatment guidelines.[94] ICS can be used in combination with other agents such as long-acting inhaled β_2-adrenoceptor agonists to provide effective asthma control in patients with persistent asthma not adequately controlled on ICS alone. Thus, ICS and β_2-adrenoceptor agonists remain the cornerstones of modern asthma therapy, including that of AIA.

Evidence from clinical trials suggests a role for LT-modifying drugs in AIA management.[95,96] Currently available drugs either inhibit cys-LT synthesis by blocking 5-lipoxygenase (zileuton) or by blocking the specific cys-LT_1 receptor (zafirlukast, montelukast and pranlukast). AIA patients taking montelukast showed an improvement in forced expiratory volume in 1 second (FEV_1), morning peak expiratory flow rate (PEFR) and asthma-specific quality of life, as well as 54% fewer exacerbations and a reduction in bronchodilator use compared with a placebo group.[96] Addition of zileuton to existing therapy in AIA patients resulted in improved pulmonary function, less use of rescue medication, improvement in symptoms and inhibition of aspirin-induced bronchoconstriction.[97] Patients with AIA show an improvement with zafirlukast treatment on spirometric and clinical criteria, associated with a decrease in urinary LTE_4 excretion, suggesting an interruption of the pulmonary chronic inflammatory process.[98] In patients with AIA, pranlukast suppressed aspirin-induced IAR and inhibited the increase of the level of sputum ECP, but failed to change aspirin-induced cys-LT production in the sputum and urine.[40] Bronchodilatation has also been observed after treatment with LT-modifying drugs, indicating that cys-LTs have an effect on basal bronchomotor tone in AIA.[97]

Although several studies showed that pre-treatment with LT-modifying drugs attenuated aspirin-provoked nasal and bronchial reactions in most patients,[99-102] a recent clinical study showed that during oral aspirin challenges, LT-modifying drugs appeared to shift target organ responses from both upper and lower respiratory tracts to upper respiratory tract alone.[103] Moreover, all studies were performed with prior established provoking doses of aspirin; however, the study by Pauls et al.[104] reported that higher therapeutic doses of aspirin overcame protection from pre-treatment with zileuton. Volkman and Pontikes[105] have reviewed four studies investigating the use of LT modifiers to prevent AIA. The efficacy of these agents ranged from complete inhibition to no blockade and they concluded that patients with AIA should be cautious when taking aspirin and NSAIDs, despite treatment with LT-modifying drugs. LT-modifying drugs may be used as adjunctive therapy for all levels of disease severity because they are effective in combination with ICS during long-term maintenance therapy. However, patients with AIA tend to have an aggressive disease course, and most patients will require standard combination therapy plus LT modifiers and, in some instances, aspirin desensitisation.

It is important to mention here the possible relationship between the LT modifiers and Churg-Strauss syndrome (CSS). There have been a number of case reports of the development of CSS following introduction of LT modifiers in the treatment of asthma.[106,107] One proposed mechanism is that the introduction of LT modifiers allows reduction in the dose of corticosteroids in patients with AIA, thereby

unmasking pre-existing disease. This is the conclusion of two reviews on the subject.[108,109] However, there are reports of CSS in association with LT modifiers in patients who were not receiving oral corticosteroids or ICS,[110,111] and the topic remains controversial.

To prevent life-threatening reactions, patients with AIA should avoid aspirin and other analgesics that inhibit COX-1; no form of aspirin, even controlled-release, should be prescribed for patients with AIA because it may provoke symptoms of aspirin intolerance.[112] If necessary, patients can usually take drugs devoid of anti-COX activity such as paracetamol (acetaminophen). However, paracetamol is reported to cross-react with aspirin in a dose-dependent way,[113] though the incidence of cross-sensitivity to paracetamol in AIA patients is low and, when a reaction does occur, the symptoms experienced are shorter and milder than if the reactions were evoked by NSAIDs.[114]

In order to overcome adverse effects of aspirin several strategies have been followed, among them the development of selective COX-2 inhibitors. Rapidly growing evidence indicates that highly specific COX-2 inhibitors are well tolerated and much less likely to cause AIA in susceptible patients.[50-52,114] Selective COX-2 inhibitors are theoretically safer for patients with AIA because constitutive COX-1 will continue to synthesise the protective prostanoid, PGE_2.[52,115,116]

Another strategy involves administering aspirin or NSAIDs to patients with AIA. A state of aspirin tolerance can be induced and maintained by aspirin desensitisation. Small incremental oral doses of aspirin are ingested over the course of 2–3 days until 400–650mg is tolerated. Aspirin can then be administered daily to maintain desensitisation.[117] During the state of desensitisation the patients usually experience improvement in their chronic respiratory symptoms and signs, especially in the nose.[118] Typically, desensitisation is indicated in patients with AIA who have just completed sinus/polyp surgery to delay recurrence.[119] The mechanism of aspirin desensitisation in patients with AIA is only partially understood. It may lead to reduction of airway responsiveness to LTE_4 because of downregulation of cys-LT_1 receptors.[87,88] At acute desensitisation, urinary cys-LT levels are the same as baseline levels and are, therefore, clearly available for stimulation of cys-LTs receptors. In a study by Juergens et al.[120] desensitisation followed by long-term treatment with aspirin resulted in decreased peripheral monocyte LTB_4 production and continued inhibition of COX enzymes. Patients maintained for months in a state of aspirin desensitisation still responded to oral aspirin challenge with a rise in LTE_4 urinary excretion, although the responses were blunted when compared with the original aspirin challenge, and the patients were all asymptomatic.[121]

Inhaled sodium cromoglicate was reported to protect against aspirin-induced attacks of asthma through mechanisms related to improvement of bronchial hypersensitivity.[122] After 1 week's treatment with sodium cromoglicate, patients' symptoms, blood and sputum eosinophil counts, and sputum ECP levels were significantly decreased compared with both placebo and baseline.

The long-acting β_2-adrenoceptor agonist salmeterol has been reported to protect against AIA through a mechanism that seems unrelated to its bronchodilator properties. Salmeterol effectively prevented bronchial reactions to inhaled aspirin-lysine in patients with AIA.[123] It also attenuated the expected aspirin-provoked rise in urinary excretion of LTE_4 and PGD-M, the major urinary metabolite of PGD_2. This may indicate direct inhibition of cys-LT metabolism by salmeterol, unique to patients with asthma with aspirin intolerance, as the same effect is not seen in all patients with asthma,[124] although it may also be related to the action of salmeterol as a mast cell stabiliser.

3.1 Potential Future Treatment Strategies

As mentioned before, aspirin-induced reactions in AIA are likely to be due to inhibition of COX with subsequent release of 5-lipoxygenase from the inhibitory effect of PGE_2. Other strategies involve the design of anti-inflammatory compounds with 5-lipoxygenase inhibitory effects. Licofelone

(ML 3000) is an anti-inflammatory compound with potent activity in various animal experiments that represent models for acute and chronic inflammation, pain, fever and asthma.[125] It is a balanced inhibitor of the enzymes 5-lipoxygenase and COX in the submicromolar range. The compound demonstrates excellent gastrointestinal tolerance in various animal species. An alternative approach is the use of nitrosylated aspirin (NO-aspirin) derivatives. A recent study by Gray et al.[126] showed that NO-aspirin, unlike other NSAIDs tested, inhibited 5-lipoxygenase activity as well as COX-1 activity *in vitro* in blood taken from both aspirin-sensitive and aspirin-tolerant individuals. Thus, there was no concomitant rise in LTs with COX-1 inhibition. This suggests that NO-aspirin may be better tolerated than aspirin by aspirin-sensitive asthmatics. However, there are no *in vivo* data in asthmatic patients with this compound to date.

4. Conclusion

Aspirin is one of the most widely used medications in the world. Adverse effects related to aspirin use were described almost concurrently with its first use. The most common adverse effects are gastrointestinal and renal, but adverse respiratory effects are not uncommon, and approximately 4–10% of adult patients with asthma are aspirin intolerant. Many of these patients present with the so-called aspirin triad of aspirin sensitivity, chronic rhinosinusitis with associated nasal polyposis and severe asthma. Aspirin provocation tests with improved diagnostic accuracy have been developed, although no *in vitro* test has been found to be of diagnostic value. At the biochemical level, AIA is characterised by a chronic overproduction of cys-LTs. Accumulated evidence shows that AIA is due to the interference of aspirin-like drugs with AA metabolism in the lungs of sensitive patients; inhibition of COX is accompanied by overproduction of cys-LTs.

Although we have gained a great deal of knowledge on the pathophysiology of AIA, a number of questions remain unanswered. Further investigation of the role of COX isoforms, lipoxygenase pathway enzymes and their products in regulating airway function may shed light on these over the next 5–10 years.

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