Aspirin desensitization in patients with aspirin-induced and aspirin-tolerant asthma: A double-blind study

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Background: Numerous open trials have demonstrated the beneficial clinical effects of aspirin desensitization (AD) in patients with aspirin-induced asthma (AIA). These beneficial effects might be attributable to aspirin’s potent anti-inflammatory properties, but that supposition requires further corroboration.

Objective: We sought to compare the clinical and biochemical responses to chronic oral AD in 20 patients with AIA and 14 patients with aspirin-tolerant asthma (ATA). All of the patients had chronic rhinosinusitis and nasal polyposis, and these responses were investigated in a pilot, double-blind, placebo-controlled study.

Methods: Twelve patients with AIA and 6 patients with ATA were randomly assigned to receive 624 mg of aspirin, and 8 patients with AIA and 8 patients with ATA received placebo. Both aspirin and placebo were administered once daily for 6 months. Nasal symptoms, Sino-Nasal Outcome Test (SNOT20) scores, peak nasal inspiratory flows, Asthma Control Questionnaire scores, spirometric parameters, peak expiratory flows, blood eosinophilia, and corticosteroid doses were assessed on a monthly basis. Levels of urinary leukotriene E4 and the stable plasma prostaglandin (PG) D2, metabolite 9α,11β-PGF2 were evaluated at baseline and after 1, 3, 5, and 6 months.

Results: Only the patients with AIA subjected to AD reported improvements in smell and reductions in sneezing and nasal blockade. The SNOT20 and Asthma Control Questionnaire scores of these patients decreased, and their peak nasal inspiratory flows increased. The dosages of inhaled corticosteroids were reduced. There were no changes in leukotriene E4 or 9α,11β-PGF2 levels after AD.

Conclusion: The clinically beneficial effects of AD on nasal and bronchial symptoms occurred only in the patients with AIA. (J Allergy Clin Immunol 2014;134:883-90.)

Key words: Aspirin-induced asthma, aspirin-tolerant asthma, oral aspirin desensitization

Aspirin-induced asthma (AIA) (also called aspirin-exacerbated respiratory disease) is a clinical syndrome consisting of asthma, rhinosinusitis with nasal polyps, and hypersensitivity to aspirin (acetylsalicylic acid [ASA]) and/or other nonsteroidal anti-inflammatory drugs (NSAIDs) that block COX-1. Complex alterations in the eicosanoid pathway that involve the overproduction of proinflammatory cysteinyl leukotrienes (cysLTs) and prostaglandin (PG) D2 and decreased synthesis of anti-inflammatory PGE2 and lipoxins have been reported in patients with AIA. Aspirin desensitization (AD) can improve rhinosinusitis and the course of uncontrolled asthma in patients with AIA. Many authors have investigated AD with different protocols and routes of administration. However, the most notable work in this field is credited to the group from the Scripps Clinic in La Jolla, California. In 1984, Stevenson et al reported clinical improvements in 25 patients with AIA after 3 months of AD in a double-blind crossover study. However, this study did not include any patients with aspirin-tolerant asthma (ATA) to facilitate the analysis of the specificity of AD. Subsequently, larger retrospective and open studies were published. Most of these studies assessed the influence of AD on the alterations of eicosanoid metabolism that have been implicated in the pathogenesis of AIA. The effects of AD might be attributable to the potent anti-inflammatory action of aspirin. A prospective, double-blind, parallel-group, placebo-controlled study assessing the clinical effects and alterations of the eicosanoid pathway caused by oral AD in both the AIA and ATA groups is still pending. If proved effective, AD might also be of great value in patients with ATA accompanied by rhinosinusitis and nasal polyps.

Therefore we studied the clinical and biochemical responses to a 6-month oral AD regimen in 20 patients with AIA and 14 patients with ATA in a pilot double-blind, placebo-controlled study.

METHODS

Patients

The inclusion criteria were as follows: (1) age of 18 to 65 years; (2) asthma diagnosed in compliance with applicable guidelines; (3) rhinosinusitis with nasal polyps as evidenced by medical records and endoscopic findings, computed tomographic (CT) findings, or both; (4) a positive history of a prior reaction to aspirin, other NSAIDs, or both confirmed by a positive...
response to oral aspirin challenge for the patients with AIA; and (5) a negative history of aspirin hypersensitivity and a negative response to aspirin challenge for the patients with ATA. The exclusion criteria were as follows: (1) a history of life-threatening anaphylactic reactions precipitated by NSAIDs; (2) uncontrolled asthma, FEV₁ of less than 70% of predicted value, or both; (4) autoimmune diseases; (5) severe diseases of the heart or digestive, respiratory, or neurologic systems or any other clinical condition that could potentially influence the study outcome; (6) neoplasm; and (7) pregnancy. Leukotriene modifiers, omalizumab, and immunotherapy or other immunomodulator drugs were prohibited throughout the study.

**Trial design**

All patients provided written informed consent in which they indicated that they had been informed that they might or might not benefit from the AD and that it is not known whether the effects of the potent anti-inflammatory drug aspirin are beneficial to patients with ATA. The study was approved by the local bioethics review committee. The study was a randomized, double-blind, placebo-controlled, parallel-group study. A total of 109 patients were randomized (by using random number tables) to a 6-month oral AD (Fig 1). Ten of the 44 eligible patients did not enter the study (4 had preplanned sinus surgeries, 5 withheld their consent for the study, and 1 had a positive response to placebo challenge). In total, 34 patients underwent a sinus surgery, 5 withheld their consent for the study, and 1 had a positive response to oral aspirin challenge for the patients with AIA; and (5) a negative history of aspirin hypersensitivity and a negative response to aspirin challenge for the patients with ATA. The exclusion criteria were as follows: (1) a history of life-threatening anaphylactic reactions precipitated by NSAIDs; (2) uncontrolled asthma, FEV₁ of less than 70% of predicted value, or both; (4) autoimmune diseases; (5) severe diseases of the heart or digestive, respiratory, or neurologic systems or any other clinical condition that could potentially influence the study outcome; (6) neoplasm; and (7) pregnancy. Leukotriene modifiers, omalizumab, and immunotherapy or other immunomodulator drugs were prohibited throughout the study.

**Aspirin challenge and desensitization**

Oral aspirin challenges were conducted. On the first day, placebo was administered 4 times every 1.5 hours. On the second day, the patients received 4 increasing doses of aspirin every 1.5 hours (27, 44, 117 and 312 mg; cumulative aspirin dose, 500 mg). Clinical symptoms, such as dyspnea, rhinorrhea, nasal blockade, sneezing, ocular secretion, and skin flushing, were assessed. Serial spirometry (abcPneumo 2000RS; abcMED, Krakow, Poland) and peak nasal inspiratory flow (PNIF; the YouTel pH/PNIFmeter, Clement Clarke International, Harlow, United Kingdom) measurements were performed every 30 minutes. Positive reactions to aspirin were defined by the appearance of clinical symptoms accompanied by decreases of at least 20% in FEV₁ relative to baseline values.

**Randomization to AD or placebo administration**

On the day after the aspirin challenge, the 12 patients with AIA randomized to the AD group (AIA-ASA) received the maximal dose of aspirin they had tolerated during the aspirin challenge. If the patient remained asymptomatic, this dose was followed by administrations of the incrementally higher dose of aspirin 1.5 hours apart until the daily cumulative dose of at least 624 mg was reached. If a patient demonstrated a clinical reaction to this dose or a 20% decrease in FEV₁ occurred before the cumulative dose of 624 mg of aspirin was reached, AD was restarted the following day with the dose that had provoked the reaction the day before. Consequently, the day of “acute desensitization” was defined as the day on which the patient was able to ingest a single daily dose of 624 mg of aspirin in the morning without any reaction (this usually took 1-3 days). That day was also the first day of chronic AD, which was then pursued for up to 6 months.

The six patients with ATA randomized to AD (ATA-ASA) were given 624 mg of aspirin once daily on the day after their negative response to the aspirin challenge and continued this daily dose for 6 months. The other 8 patients with AIA (AIA-placebo) and 8 patients with ATA (ATA-placebo) were randomized to placebo administration for 6 months and received placebo on the day after the aspirin challenge.

**Assessments**

**Clinical evaluations.** At baseline and during the AD or placebo administration procedures (6 visits [V1-V6] every 30 ± 7 days), the patients were examined by a blinded physician. Asthma Control Questionnaire (ACQ) and Sino-Nasal Outcome Test (SNOT20) scores were analyzed, and FEV₁, peak expiratory flow (PEF; Mini-Wright Peak Flow Meter, Clement Clarke International; best of 3 efforts), and PNIF values were measured. Doses of inhaled corticosteroids (ICSs) and nasal corticosteroids were kept stable and Sino-Nasal Outcome Test (SNOT20) scores were analyzed, and FEV₁, peak expiratory flow (PEF; Mini-Wright Peak Flow Meter, Clement Clarke International; best of 3 efforts), and PNIF values were measured. Doses of inhaled corticosteroids (ICSs) and nasal corticosteroids were kept stable throughout the aspirin challenge and acute desensitization; during the 6-month course of chronic AD, these doses were altered according to the clinical status of the patients. The patients also completed diaries with scores for nasal (smell, nasal blockade, sneezing, rhinorrhea, postnasal drip, and nasal itching) and bronchial (cough and dyspnea) symptoms that were assessed on a visual analog scale (0, none; 10, the most severe). All adverse events were duly recorded. Before entering the trial, all but 1 patient underwent spiral CT scans of the sinuses (ElScint Flash, Haifa, Israel), and the results were evaluated by an experienced radiologist according to the Lund-Mackay score. In 21 patients sinus CT scans were repeated after 6 months (for details, see the Results section).

**Laboratory evaluations.** Urine samples were collected for the assessment of leukotriene E₂ (LTE₂) excretion at baseline and after 6 hours on the first day (placebo) and on the following day (aspirin challenge). Samples were also collected on the day of acute AD and during the actual visits in the first (V1), third (V3), fifth (V5), and sixth (V6) months of AD or placebo administration. Urinary LTE₂ (uLTE₂) levels were assessed with the enzyme immunoassay method (Cayman Chemicals, Ann Arbor, Mich). Blood plasma was taken to assess 9α,11β-prostaglandin F₂ (9α,11β-PGF₂) levels at the same time points. Gas chromatography–negative ion chemical ionization mass spectrometry (model 5896 series II; Hewlett Packard, Palo Alto, Calif) was used to measure 9α,11β-PGF₂ levels. In 21 patients sinus CT scans were repeated after 6 months (for details, see the Results section).

**Statistical analyses**

The primary end points of the study were the following: the clinical efficacy of AD (ie, the changes in the scores for the clinical symptoms); PNIF, FEV₁, and PEF values; and absolute reductions in corticosteroid doses. The secondary end points were changes in uLTE₂, p9α,11β-PGF₂, or both levels after AD. Statistical evaluations were performed with STATISTICA 10 software (StatSoft, Tulsa, Okla) for Windows. Summary statistics are expressed as the median and interquartile range in the tables when not otherwise stated. One-way and multi-way ANOVAs with the Tukey post hoc procedure for testing multiple comparisons were used to compare the groups during AD (only significant results, expressed as the mean and SD, are listed in the Results section). Logarithmic transformations were used to stabilize variance. Mann-Whitney
**RESULTS**

**Patients**

Twenty-eight of the 34 patients completed the 6-month AD or placebo administration regimen (AIA-ASA: \( n = 8 \), AIA-placebo: \( n = 7 \), ATA-ASA: \( n = 5 \), ATA-placebo: \( n = 8 \); Fig 1; for the reasons for discontinuation, see the section on the adverse events related to AD). The patient groups were comparable in the majority of baseline characteristics (Tables I and II). Selected specific outcomes of the subjects are presented in Table E1 in this article’s Online Repository at www.jacionline.org.

**Clinical evaluations**

Chronic AD resulted in significant improvements in asthma control and less intensive therapy only for the patients with AIA (AIA-ASA). By the sixth month of chronic AD (ie, at visit 6), ACQ scores decreased in the AIA-ASA group compared with those in the AIA-placebo group (\( P = .037 \), Fig 2). The ICS doses of the AIA-ASA group were also lower than those of the AIA-placebo group (\( P = .03 \), Fig 2). Asthma symptoms, FEV\(_1\) and PEF values, and use of rescue medications did not change in any studied group throughout the 6-month chronic AD course. There were no hospitalizations caused by asthma exacerbation.

AD diminished the severity of rhinosinusitis only in the patients with AIA. Compared with baseline, SNOT20 scores decreased at visits V1 (\( P = .001 \)), V2 (\( P = .002 \)), V3 (\( P = .08 \)), V4 (\( P = .04 \)), and V5 (\( P = .04 \)) only in the AIA-ASA group, and these values remained unaltered in the other 3 groups (Fig 3). At V6, PNIF values increased compared with baseline values only in the AIA-ASA group (\( P = .001 \), Fig 3). Improvements in smell were observed in 5 of the 8 patients with AIA after 6 months of AD (2 of the 7 taking placebo exhibited improvements in smell). Smell scores on V1 and V6 were lower than those at baseline only in the AIA-ASA group (\( P = .01 \) and .046, respectively; see Fig E1 in this article’s Online Repository at www.jacionline.org). Sneezing scores decreased significantly compared with those at baseline at V1 (\( P = .02 \)), V3 (\( P = .005 \)), V4 (\( P = .02 \)), and V5 (\( P = .02 \)), and nasal blockade decreased significantly compared with that seen at baseline at V2 (\( P = .049 \)) in only the AIA-ASA group (see Fig E1). Baseline sinus CT scores were higher in the patients with AIA (\( n = 20 \)) than in the patients with ATA (\( n = 13 \); 18.0 ± 5.0 vs 12.9 ± 5.3, respectively; \( P = .01 \)). Twenty-one of the 28 patients who completed the study agreed to undergo an additional sinus CT scan. The CT scores were similar to those at baseline in 7 patients in the AIA-ASA group (20.3 ± 3.1 and 19.7 ± 3.7, respectively; \( P = .76 \)); 5 patients in the ATA-ASA group (17.8 ± 5.7 and 17.4 ± 5.2, respectively; \( P = .84 \)), 3 patients in the AIA-placebo group (15.0 ± 1.0 and 15.7 ± 1.5, respectively; \( P = .45 \)), and 6 patients in the ATA-placebo group (10.2 ± 4.7 and 11.2 ± 6, respectively; \( P = .65 \)).

**Laboratory evaluations**

**Aspirin challenge.** The responses to aspirin challenge were positive in all 20 patients with AIA and negative in all 14 patients...
with ATA. The mean aspirin provocative dose of the AIA group was 287 ± 616 mg. The mean baseline uLTE₄ level of the AIA group was significantly higher than that of the ATA group (3794.5 ± 7355.4 vs 1439.6 ± 2722.0 pg/mg creatinine, respectively; \( P = .01 \); Fig 4). Compared with baseline, excretion of uLTE₄ exhibited further increases only in the AIA group after

**TABLE II.** Clinical characteristics of the 4 groups of patients: patients with AIA receiving AD (AIA-ASA), patients with AIA receiving placebo (AIA-placebo), patients with ATA receiving aspirin therapy (ATA-ASA), and patients with ATA receiving placebo (ATA-placebo)

<table>
<thead>
<tr>
<th></th>
<th>AIA-ASA (n = 12)</th>
<th>AIA-placebo (n = 8)</th>
<th>P value</th>
<th>ATA-ASA (n = 6)</th>
<th>ATA-placebo (n = 8)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>48.5 ± 18.0</td>
<td>39.5 ± 27.0</td>
<td>.79</td>
<td>50.0 ± 23.0</td>
<td>49.0 ± 15.0</td>
<td>.75</td>
</tr>
<tr>
<td>Sex (female/male ratio)</td>
<td>9/3</td>
<td>6/2</td>
<td>1.0</td>
<td>1/5</td>
<td>2/6</td>
<td>1.0</td>
</tr>
<tr>
<td>Aspirin hypersensitivity duration (y)</td>
<td>11.0 ± 6.5</td>
<td>6.0 ± 4.5</td>
<td>.07</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Asthma duration (y)</td>
<td>8.5 ± 10.0</td>
<td>7.0 ± 3.0</td>
<td>.27</td>
<td>7.5 ± 6.0</td>
<td>5.5 ± 6.5</td>
<td>.49</td>
</tr>
<tr>
<td>Rhinitis duration (y)</td>
<td>16.0 ± 8.0</td>
<td>7.5 ± 7.5</td>
<td>.13</td>
<td>17.5 ± 9.0</td>
<td>8.5 ± 10.0</td>
<td>.14</td>
</tr>
<tr>
<td>Nasal polyposis duration (y)</td>
<td>10.1 ± 8.5</td>
<td>6.0 ± 9.0</td>
<td>.47</td>
<td>14.0 ± 19.0</td>
<td>1.5 ± 7.0</td>
<td>.18</td>
</tr>
<tr>
<td>No. of polypectomies per patient</td>
<td>3.5 ± 8</td>
<td>1.5 ± 2.0</td>
<td>.27</td>
<td>2.5 ± 3.0</td>
<td>1.0 ± 1.5</td>
<td>.28</td>
</tr>
<tr>
<td>ICSs (( \mu g ))*</td>
<td>800 ± 600</td>
<td>800 ± 650</td>
<td>.43</td>
<td>800 ± 800</td>
<td>600 ± 450</td>
<td>.75</td>
</tr>
<tr>
<td>Baseline FEV₁ (% predicted)</td>
<td>84.6 ± 23.0</td>
<td>93.9 ± 14.2</td>
<td>.52</td>
<td>92.5 ± 23.7</td>
<td>95.7 ± 29.9</td>
<td>.66</td>
</tr>
<tr>
<td>Baseline PEF (L/min)</td>
<td>445 ± 148</td>
<td>405 ± 110</td>
<td>.79</td>
<td>357.5 ± 10</td>
<td>540 ± 170</td>
<td>.03</td>
</tr>
<tr>
<td>Baseline PNIF (L/min)</td>
<td>135 ± 110</td>
<td>125 ± 100</td>
<td>.79</td>
<td>190 ± 70</td>
<td>195 ± 165</td>
<td>.95</td>
</tr>
<tr>
<td>Eosinophil blood count (/mm³)</td>
<td>429 ± 642</td>
<td>639 ± 299</td>
<td>.38</td>
<td>352.5 ± 288</td>
<td>218 ± 359</td>
<td>.37</td>
</tr>
<tr>
<td>SNOT20</td>
<td>1.9 ± 0.8</td>
<td>1.8 ± 1.2</td>
<td>.73</td>
<td>1.8 ± 1.5</td>
<td>1.1 ± 0.6</td>
<td>.04</td>
</tr>
<tr>
<td>ACQ score</td>
<td>1.2 ± 2.0</td>
<td>1.4 ± 1.1</td>
<td>.68</td>
<td>1.1 ± 0.7</td>
<td>0.7 ± 1.1</td>
<td>.41</td>
</tr>
<tr>
<td>Serum IgE (IU/mL)</td>
<td>75.0 ± 66.5</td>
<td>38.0 ± 153</td>
<td>.27</td>
<td>113.1 ± 90.2</td>
<td>107.0 ± 127.3</td>
<td>.95</td>
</tr>
</tbody>
</table>

Values are expressed as medians ± interquartile ranges.

NA, Not applicable.

\*Daily dose presented as budesonide equivalent.
aspirin challenge (5445.1 ± 8312.9 vs 3794.5 ± 7355.4 pg/mg creatinine, respectively; \(P < .001\); Fig 4).

The mean baseline p9α,11β-PGF2 level of the AIA group was significantly higher than that of the ATA group (5.77 vs 3.1 ± 1.1 pg/mL, respectively; \(P = .03\)), and no further increases after aspirin challenge were observed (Fig 4).

Six-month chronic AD or placebo intake. The baseline uLTE4 levels of both the AIA-placebo and AIA-ASA groups were higher than that of the ATA-placebo group (7439.8 ± 10970.3 and 1364.3 ± 869.3 vs 724.7 ± 565.8 pg/mg creatinine; \(P = .002\) and \(P = .007\), respectively) and similar to that of the ATA-ASA group (2392.8 ± 4112.2 pg/mg creatinine). Neither chronic AD nor placebo intake altered uLTE4 levels in any of the 4 groups (Fig 5).

The p9α,11β-PGF2 levels and blood eosinophil counts, analyzed separately within the 4 groups, were comparable at baseline and across the 6-month AD or placebo intake period (Fig 5).

Adverse events related to AD. In total, 6 study subjects dropped out of the study (Fig 1). One patient with AIA in the placebo group dropped out because of the lack of improvement. Five patients (4 patients with AIA and 1 patient with ATA) dropped out because of dyspepsia during chronic AD. One patient with AIA also had a transient skin rash.

**DISCUSSION**

In recent decades, several observational studies and 1 double-blind study (without an ATA control group) have demonstrated the clinical efficacy of oral AD in patients with AIA. Oral AD improves nasal and bronchial symptoms; patients require fewer corticosteroids and antibiotics for upper respiratory tract infections and fewer emergency department visits, hospitalizations, outpatient visits, and sinus surgeries. Moreover, open observations of nasal desensitization have revealed that lysine-aspirin (L-ASA) reduces the frequency of nasal polyp relapse and increased PNIF values in patients with AIA compared with values seen in untreated control subjects.

Nevertheless, the first double-blind crossover trial of patients with AIA (22 patients) did not demonstrate any significant improvement in acoustic rhinometry parameters, PNIF values, PEF values, or symptom scores after 6 months of nasal L-ASA desensitization. Thus the positive effects of AD have typically been observed in uncontrolled trials. It was also previously unclear whether a beneficial effect of AD would be observed only in patients with AIA. Improvements in patients with AIA and those with ATA after open nasal L-ASA desensitization have been reported.

Recent studies have demonstrated the newly discovered properties of aspirin in regulating the immune system that extend beyond those related to COX inhibition. Aspirin inhibits T-cell proliferation, cytokine production, activation of NF-κB during transcription of proinflammatory cytokines, and antibody production.

Our pilot, prospective, placebo-controlled parallel-group study is the first to prove that the positive effect of oral AD might only occur in patients with AIA.

We demonstrated that 6 months of chronic oral AD led to clinical improvements in asthma control in patients with AIA; these improvements were expressed as decreases in ACQ scores and reductions in ICS doses. Asthma improvement has also been observed in an open study during a 6-month AD course. In contrast to the aforementioned study, we were able to detect a favorable effect of AD only on maintenance doses of ICSs. This discrepancy might be attributable to the fact that the other investigators used a dose of ASA (1300 mg) that was twice that of the dose used here.

Similar to other reports, our patients with AIA receiving AD therapy reported long-lasting returns of their sense of smell relatively early. In our study sneezing and nasal blockade scores decreased significantly only in the AIA-ASA group, and the majority of relevant studies have reported similar results. Furthermore, we demonstrated that scores on the well-standardized SNOT20 decreased significantly only in the AIA-ASA group, which effectively corroborates the results of Katial et al.
Notably, we used objective outcome measurements (eg, nasal and pulmonary function tests and sinus CT scans) that have seldom been used to evaluate the effects of AD. Six months of AD resulted in significant improvements in PNIF values in our patients with AIA, but FEV1 and PEF values remained unaltered. To the best of our knowledge, the present study is the first to assess sinus CT scans in patients undergoing AD. Unfortunately, no improvements were observed in Lund-Mackay scores. Similarly, another study that used radiographs of the paranasal sinuses observed no obvious effects on these images after AD.14 The relatively short duration of AD and the small number of CT scans analyzed might account for this discrepancy. Six months of AD might be insufficient to detect differences in numbers of sinus surgeries because these differences tend to become evident within at least 1 year of the actual therapy.33 The effect of AD is more evident when the occurrences of nasal polyp relapses after surgery are evaluated.24,31,33 Our patients were not directly subjected to sinus surgeries before AD. Most of our patients were reluctant to undergo surgery because nearly all had undergone multiple previous surgeries.

The overproduction of eicosanoids at both baseline and after aspirin challenge is a well-known feature of AIA that correlates with the severity of the reaction to aspirin.1-3,44 Therefore it would be reasonable to expect that AD should decrease eicosanoid production. In our study AD did not decrease uLTE4 or p9α,11β-PGF2α levels. Nevertheless, Nasser et al30 observed a substantial increase in LTE4 excretion that continued up to 9 months of oral AD. Oral AD decreases peripheral monocyte synthesis of LTB4 but not LTC4.29 The actual mechanisms underlying the process of AD might be quite independent from baseline cysLT biosynthesis and might be attributable to decreases in the sensitivities of the airways to LTE4.45 The mechanism might also involve changes in the numbers of leukotriene receptors after AD,16 which could be related to the downregulation of IL-4 production.22 Interestingly, recent studies have demonstrated that AD might decrease the IL-4 levels that are deemed responsible for the upregulation of LTC4 synthase by mast cells and the upregulation of cysLT receptors on many immune cell types in patients with AIA.42 Recently, a novel mechanism for the augmentation of the transcellular

![Graph](image_url)
conversion of leukotrienes that is mediated by platelet adherence has been reported.25

Aspirin has also been postulated to exert direct effects on the biochemical pathways of mast cells.25 Chronic AD decreases serum28 and sputum22 tryptase levels. To the best of our knowledge, ours is the first report to assess the effects of AD on another important mast cell mediator, p9α,11β-PGF2α. Significant increases in p9α,11β-PGF2α levels after allergen and aspirin challenges have been observed.1,4,11,42,47 However, in our study neither the actual aspirin challenge nor the chronic AD affected p9α,11β-PGF2α levels. This discrepancy could be due to differences in mechanisms that govern the release of p9α,11β-PGF2α from mast cells and those that govern tryptase levels, or the small number of patients might have precluded the detection of possible differences.

The main limitation of our study is that the number of subjects was small. We are not the first group to encounter serious difficulties in the recruitment of patients for double-blind studies of AD. A recently published systematic review of the literature related to nasal outcomes of AD in patients with aspirin-exacerbated respiratory disease found that only 11 of 614 citations met the criteria for analysis and that most of the studies had small sample sizes.31 In the first double-blind study, 25 patients with AIA served as their own control subjects by taking 3 different doses of aspirin or placebo for 3 months (there was no parallel ATA group).26 Seven patients took 1 tablet (325 mg of aspirin), 5 patients took 4 tablets, and 13 patients took 8 tablets.26 These numbers are not much greater than those (325 mg of aspirin), 5 patients took 4 tablets, and 13 patients took 8 tablets.26

In conclusion, in this pilot double-blind study we observed moderate and specific beneficial effects of a 6-month AD treatment on bronchial and nasal symptom scores, ICS maintenance doses, and PNIF values that were limited to the patients with AIA. Larger controlled studies of longer duration assessing the efficacy, safety profile, and specific mechanisms of AD, particularly in terms of objective measurements, are therefore strongly recommended.

Key messages
- Chronic oral AD significantly improved the control of rhinosinusitis and asthma.
- The beneficial effects of chronic oral AD were observed only in the patients with AIA.

REFERENCES


