Long-term treatment with aspirin desensitization in asthmatic patients with aspirin-exacerbated respiratory disease

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Background: Aspirin desensitization treatment is an option to decrease disease activity and reduce the need for systemic corticosteroids in patients with aspirin-exacerbated respiratory disease (AERD).
Objective: This study was designed to determine whether the clinical courses of patients with AERD improved as early as 6 months after starting aspirin desensitization and to compare this with follow-up evaluations after at least a year.
Methods: Between 1995 and 2000, 172 patients with AERD were admitted to our General Clinical Research Center, were desensitized to and treated with aspirin, were discharged to their home communities, and participated in follow-up interviews and written assessments of their clinical courses.
Results: By the first 6 months of aspirin treatment, there were significant reductions in sinus infections and numbers of short courses of prednisone and improvements in sense of smell and general assessment of nasal-sinus and asthma symptoms ($P < .0001$). These results persisted for 1 to 5 years ($P < .0001$). Mean prednisone doses decreased from 10.8 mg/d to 8.1 and 3.6 mg/d at 6 months and greater than 1 year, respectively. Of the 172 patients, 24 (14%) discontinued aspirin treatment because of side effects, and 115 (67%) responded to aspirin treatment. After eliminating those who discontinued aspirin treatment because of side effects, the improvement rate was 115 (78%) of 148 patients. Of the 126 patients who completed a year or more of aspirin treatment, 110 (87%) experienced improvement.
Conclusion: Aspirin desensitization followed by daily aspirin is efficacious by at least the first 6 months of treatment and continues to be effective for up to 5 years of follow-up. (J Allergy Clin Immunol 2003;111:180-6.)

Key words: *Aspirin, asthma, rhinitis, desensitization, nonsteroidal anti-inflammatory drugs, aspirin desensitization treatment*

Abbreviations used
AERD: Aspirin-exacerbated respiratory disease
GCRC: General Clinical Research Center
LTMD: Leukotriene modifier drug
LTRA: Leukotriene receptor antagonist

In 1922, Widal et al[1] conducted aspirin desensitization in one aspirin-sensitive asthmatic patient, and in 1976, Zeiss and Lockey[2] desensitized another patient to indomethacin. In 1980, Stevenson et al[3] reported that 2 patients with aspirin-exacerbated respiratory disease (AERD)[4] were desensitized to aspirin. Both patients were treated with 325 mg of aspirin twice daily and, during the next year, experienced improvement in nasal symptoms, reduction in sinusitis episodes, and reduction in need for systemic corticosteroids.

Since then, 4 studies have reported that after aspirin desensitization and daily aspirin treatment, the majority of patients with AERD experience improvement in their chronic respiratory symptoms.[5-8] In our 1984 study,[5] we showed a higher percentage of responders (69%) in the study patients receiving 650 mg of aspirin twice daily than in those taking 325 mg/d (57%) or 325 mg twice daily (60%). In 1996, Stevenson et al[8] reported that 65 patients with AERD who were treated with an average of 1300 mg of aspirin daily experienced significant improvement in their disease symptoms and reduction in use of systemic and nasal corticosteroids when evaluated at 1 to 3 years and 3 to 6 years later. The purpose of this current study was to determine whether patients with AERD experienced improvement in their disease during the first 6 months of aspirin treatment and, furthermore, whether this response persisted. Second, we sought to determine precisely how many patients experienced improvement, did not experience improvement, or had side effects from aspirin treatment after aspirin desensitization.

METHODS

Patients

Between July 1995 and July 2000, 172 patients signed consent forms approved by our human subjects committee, were admitted to our General Clinical Research Center (GCRC), underwent standard single-blind oral aspirin challenges,[9,10] experienced respiratory

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TABLE I. Analysis of changes in markers of clinical disease during the first 6 months of treatment with aspirin desensitization (n = 126)

	Baseline		Six mo after treatment		
	Median	**Range**	**Median**	**Range**	***P* value**
No. of sinus infections for 6 mo*	2.5*	0-6	1.0	0-6	<.0001
Smell scores	0.0	0-5	3.0	0-5	<.0001
Nasal symptom scores	2.0	0-4	4.0	0-4	<.0001
Asthma symptom scores	3.0	0-4	4.0	0-4	<.0001

Values were determined with Wilcoxon signed-rank statistic. Two-sided *P* values were reported.
*For comparison purposes, the rate of 5 sinus infections in the year before the study was decreased by half to compare it with the first 6 months after starting aspirin treatment.

reactions to aspirin, and completed aspirin desensitization. Patients were then discharged from the GCRC taking 650 mg of aspirin twice daily and returned to the care of their referring physicians. Reduction of systemic corticosteroids was a priority, and after a year, aspirin doses could be gradually reduced if the patient's clinical course was satisfactory. Patients with gastritis or bruising were instructed to reduce their aspirin doses earlier.

All 172 patients underwent re-evaluation of their clinical status by means of questionnaires and telephone interviews by GCRC nursing staff. These data were collected monthly during the first 6 months and then every 6 months thereafter up to 6 years for those patients who were evaluated in 1995.

Study design

Collation and analysis of data occurred in the summer of 2001 at least 1 year after the last patient enrolled in the study during July 2000. At 6 months, we determine whether aspirin desensitization treatment was or was not effective and made the same analysis for the last year of the study. Finally, we determined the clinical outcome of each patient. The following measurements were recorded.

Number of sinus infections. Sinus infection was defined as a change to purulent nasal discharge requiring antibiotics as treatment. We recorded the number of sinus infections in the year before aspirin desensitization, for the next 6 months, and in the last year after aspirin desensitization.

Number of surgical procedures. Surgical interventions to resect polypoid tissue and debride infected sinuses were recorded before desensitization and during the years of aspirin desensitization treatment. The number of surgical procedures per year before desensitization (number of interventions divided by the numbers of years of disease before desensitization) and the number of surgical procedures per year after desensitization were recorded. At 6 months, analysis was not completed because outcomes were determined per year.

Hospital admissions for asthma. The number of hospital admissions for asthma per year before desensitization and during aspirin treatment was compiled. An analysis at 6 months was too short a time to use this outcome measure.

Emergency department visits. The number of visits per year for treatment of asthma before and after admission to the study was calculated in the same manner as above.

Symptom scores for sense of smell. Subjective symptom scores for sense of smell were as follows: 0, no sense of smell; 1, intermittent partial sense of smell; 2, intermittent complete sense of smell; 3, partial sense of smell the majority of the time; 4, complete sense of smell the majority of the time; and 5, perfect and continuous sense of smell. We scored the sense of smell in the previous year of desensitization, during the first 6 months of aspirin treatment, and during the last year of follow-up.

Topical corticosteroids for nasal insufflation. We recorded the number of patients who were taking nasal corticosteroids at baseline, at 6 months, and at the last year of their aspirin treatment. For comparison and statistical analyses, doses (in micrograms per day) for those taking nasal corticosteroids were calculated for the same 3 time periods.

Topical corticosteroids for bronchial inhalation. The same treatment of data that is described for nasal corticosteroids was used for inhaled corticosteroids.

Systemic corticosteroids. For the 5 patients taking methylprednisolone, doses were converted to prednisone equivalents at a ratio of 4:5. In patients who were taking prednisone on alternate days, we calculated the daily dose equivalent by using half of the every-other-day dose. We recorded the number of patients and the average daily doses for every-other-day and daily prednisone for the year preceding aspirin desensitization, during the first 6 months of aspirin treatment, and during the last year of aspirin treatment. The numbers of bursts of prednisone per year were also calculated for the same time points.

Leukotriene modifier drugs. On January 9, 1998, the first patient who was taking a leukotriene modifier drug (LTMD) was admitted to our GCRC. After this date, all 3 LTMDs were either part of some patients' controller program at baseline or were added by their referring physicians during aspirin desensitization treatment. We recorded the number and type of LTMDs at each of the 3 time points and linked this information to the patients' clinical courses.

Global assessment of asthma activity and nasal-sinus symptoms. Subjective scores for general assessment of asthma and rhinitis-sinusitis were as follows: 1, terrible; 2, poor; 3, fair; 4, good; and 5, excellent. From these subjective scores, patients rated the state of their asthma and rhinosinusitis before desensitization, 6 months later, and in the last year.

Individual patient responses to aspirin desensitization treatment (used to determine responders or nonresponders)

An excellent response to aspirin desensitization treatment was defined as a reduction in all clinical markers for respiratory disease, improvement in both global assessment scores, and a decrease in the use of nasal, inhaled, and systemic corticosteroids. A good response was defined as a reduction in some clinical markers for respiratory disease, improvement in at least one global assessment score along with the same corticosteroid treatment, or a decrease in use of at least one of the following: nasal, inhaled, or systemic corticosteroids. An increase in use of any of the 3 corticosteroids disqualified a patient from having a good response and was classified as a treatment failure.

These patients were further subdivided into the following groups:

1. Responses in both upper and lower airways: patients experienced reduction in all clinical parameters and both global assessment scores but continued to receive the same dose of at least one of the following: nasal, inhaled, or systemic corticosteroid treatment.

TABLE II. Analysis of changes in markers of clinical disease after greater than 1 year of treatment with aspirin desensitization (n = 126)

	Baseline		≥1 y after therapy		
	Median	Range	Median	Range	*P* value
No. of sinus infections/y	5.0	0-12	2.0	0-12	<.0001
Smell scores	0.0	0-5	3.0	0-5	<.0001
Nasal symptom scores	2.0	0-4	4.0	0-4	<.0001
Asthma symptom scores	3.0	0-4	4.0	0-4	<.0001
Sinus operations/y	0.22	0-3	0.0	0-2	<.0001
Hospitalizations for asthma/y	0.0	0-5	0.0	0-3	<.0001
Emergency department visits for asthma/y	0.15	0-15	0.0	0-5	<.0001

Values were determined with the Wilcoxon signed-rank statistic. Two-sided *P* values were reported.

TABLE III. Analysis of treatment with corticosteroids before, at 6 months after, and greater than 1 year after starting aspirin desensitization therapy

	Baseline		Aspirin treatment at 6 mo			Aspirin treatment at >1 y		
	Mean	SEM	Mean	SEM	*P* value*	Mean	SEM	*P* value*
Nasal corticosteroids (μg/d)	271.4	10.3	252.2	10.5	.004	216.3	15.0	<.0001
Inhaled corticosteroids (μg/d)	867.3	52.1	829.9	49.2	.06	656.7	35.4	<.0001
Daily corticosteroids (mg/d)	10.8	1.8	8.1	1.6	.01	3.6	0.8	<.0001
Short courses of corticosteroids/y	2.7	0.7	0.8	0.9	<.0001	0.5	1.3	<.0001

Values were determined with the paired *t* test.
*Comparisons were made between baseline and 6 months and baseline and greater than 1 year.

2. Responses in upper airways: patients experienced improvement in nasosinus parameters and global assessment for nasal symptoms but continued the same assessment of asthma with the same or a decrease in at least one of the following: nasal, inhaled, or systemic corticosteroid treatment.
3. Response in lower airways: patients experienced improvement in clinical parameters and in their global asthma assessments but continued the same or a decrease in either their nasal, inhaled, or systemic corticosteroid treatment.

Nonresponders were defined as failure to experience decreases in parameters of either upper or lower airway measures, including global assessments, or improvement in clinical parameters while receiving more nasal, inhaled, or systemic corticosteroids.

Statistical analyses

The nonparametric Wilcoxon signed-rank test (Tables I and II) was used. For parametric statistics, paired *t* tests were used to analyze the changes in medications (Table III). The McNemar 2-sided test was used to determine whether there were any changes in drug use when comparing baseline values with use at 6 months and the last year of aspirin treatment (Table IV). The Fisher 2-sided exact test was used to compare the frequencies of response to aspirin desensitization in patients treated with and without LTMDs.

RESULTS

As shown in Table V, 24 (14%) of 172 patients discontinued aspirin treatment because of known side effects: 14 with pain caused by gastritis, 2 with bleeding caused by gastritis, 6 with hives, and 2 with bleeding from the nose and an ear. In the remaining group of 148 patients, 17 (11%) patients who did not have side effects from aspirin also discontinued aspirin treatment in the first year. Of these, 2 died of unrelated causes within the first 6 months of aspirin treatment, and 15 discontinued aspirin treatment in the first year for a variety of aspirin-related or aspirin-unrelated problems (viral upper respiratory tract infection, skin bruising, entering another medication trial, sneezing attacks, hoarseness, increased liver enzymes, muscle aches, or no reason given). This group of 17 patients was classified as probably failing to respond to aspirin treatment or at least discontinuing treatment. A second group of 5 (3%) of 148 patients probably responded to treatment but had to discontinue aspirin treatment use for reasons unrelated to therapeutic benefit: one patient became pregnant, and a surgeon required discontinuation of aspirin treatment for elective surgery in the other 4 patients. The pregnant patient experienced clinical improvement, and her prednisone use was decreased at the 6-month point. However, she then became pregnant and discontinued aspirin treatment. In the latter group of 4 patients, all were responders, experienced worsening symptoms after discontinuing aspirin treatment, and eventually returned to the GCRC to undergo repeat desensitization and continue daily aspirin treatment to the present. These 5 patients are classified as probable responders.

As shown in Table V, of the remaining 126 patients who took aspirin daily and were followed for at least a year, 110 (87%) enjoyed improvement in their clinical courses, and 16 (13%) did not experience improvement. At the end of the first year, for the 16 patients whose symptoms did not improve, doses of aspirin were adjusted upward for 9 of 16 patients and remained at 650 mg

TABLE IV. Number of patients who were taking systemic corticosteroids and LTMDs at baseline, at 6 months, and during the last year of aspirin desensitization treatment (n = 126)

	Baseline	6 mo after aspirin treatment	*P* value	Last year of aspirin treatment	*P* value
Not receiving prednisone	39 (31%)	62 (49%)	<.0001	84 (66%)	<.0001
Bursts of prednisone	55 (44%)	37 (29%)	<.0001	17 (13%)	<.0001
Alternate-day prednisone	2 (1%)	1 (1%)	NS	1 (1%)	NS
Daily prednisone	30 (24%)	26 (21%)	NS	24 (19%)	.03
Not receiving any LTMDs	102 (81%)	88 (70%)	.001	63 (50%)	<.0001
Zafirlukast use	7 (6%)	16 (13%)	.001	20 (16%)	<.0001
Montelukast use	13 (10%)	18 (14%)	.01	40 (32%)	<.0001
Zileuton use	4 (3%)	4 (3%)	NS	3 (2%)	NS

P values were obtained by using the 2-sided McNemar test.
NS, Not significant.

TABLE V. Total number of patients undergoing aspirin desensitization treatment

Starting treatment group	172
Discontinued aspirin treatment in the first year because of side effects	
Gastric pain	14
Gastric bleeding	2
Bleeding (nose, ear)	2
Urticaria induced by aspirin	6
Total no. of patients who discontinued aspirin treatment	24 (13%)
Remaining patients	148
Probably failed to respond to aspirin (discontinued aspirin treatment during the first year)	
Worsening respiratory symptoms	3
Died natural death (first 6 months)	2
Unclear reasons	12
Total no. who probably failed to respond	17/148 (11%)
Probable responders (discontinued aspirin treatment during the first year for other reasons)	
Planned pregnancy	1
Surgeon discontinued aspirin treatment	4
Total no. who probably responded	5/148 (3%)
Total no. who discontinued aspirin treatment during the first year	22/148 (14%)
Treatment group who took aspirin for at least a year	126
Failed to respond to aspirin desensitization treatment	
Improved but added prednisone	12
Clinically not improved	4
Total no. who did not respond to aspirin treatment	16/126 (11%)
Responded to aspirin desensitization treatment	
Excellent responders	60
Good responders	50
Total no. who responded to aspirin treatment	110/126 (87%)
Total of all responders when those with side effects were deleted	115/148 (78%)
Total of all responders when both side effects and failures were recorded	115/172 (67%)

of aspirin twice daily in the other 7 patients. Fifty-five (50%) of 110 responders took the same 650 mg of aspirin twice daily throughout the entire study period, but 49 (45%) of 110 responders had their aspirin doses adjusted downward (325-975 mg/d) at the end of the first year after experiencing excellent or good control of disease. Six of 55 patients had gastric pain during the first 6 months, and their aspirin dosages were decreased to 325 mg twice daily. All 6 also took proton pump inhibitors, continued aspirin, and experienced excellent (n = 4) and good (n = 2) responses. The mean daily dose of aspirin for all 126 patients was 1138 mg/d.

As shown in Table I, pretreatment assessments were compared with assessment at 6 months of aspirin treatment. There were highly significant ($P < .0001$) reductions in the numbers of sinus infections and improvements in sense of smell and global assessment of nasosinus and asthma symptoms. The time course was too short to analyze hospitalizations, sinus surgery rates, and emergency department visits for asthma at 6 months.

The results obtained for the patients who were treated with aspirin during 1 to 5 years are presented in Table II and continued to show significant improvement.

The other important assessment of the 126 patients was their requirements for controller medications: topical nasal and bronchial corticosteroids, systemic corticosteroids, and LTMDs. Each of these assessments is presented below and in Tables III and IV.

Topical corticosteroids for nasal insufflation

Of 126 patients, 103 (82%) were using topical nasal steroids at the time of entry into the study, with an average dose of 271.4 μg/d. The individual use of nasal steroids by the study subjects barely changed at 6 months (ie, 102/126 [81%]) but decreased significantly (ie, 61/126 [48%]) during the last year of evaluation. As shown in Table III, for those patients taking nasal steroids, the average doses decreased significantly from 271.4 to 252.2 μg/d ($P = .004$) at 6 months and to 216.3 μg/d ($P \leq .0001$) at the end of the study.

Topical corticosteroids for bronchial inhalation

Of the 126 patients, 101 (80%) were taking inhaled corticosteroids at study entry, with a mean dose of 867.3 μg/d. The number of patients who continued to take inhaled corticosteroids did not decrease significantly at either 6 months or at the end of the study (97/126 [77%] and 93/126 [74%], respectively). The daily dose of inhaled corticosteroids did decrease, although it did not reach significance at 6 months (867.3-829.9 μg/d, $P = .06$), but it did decrease significantly by the end of the study to 656.7 μg/d ($P < .0001$, Table III).

Systemic corticosteroids

As shown in Table IV, at baseline, 39 (31%) of 126 patients were not taking any systemic corticosteroids, 55 (44%) of 126 patients were receiving bursts of steroids, 2 (1%) were taking prednisone every other day, and 30 (24%) were taking prednisone daily. More patients were able to avoid systemic corticosteroids at 6 months (31% at baseline increasing to 49%), and 66% of patients were not taking systemic corticosteroids at the end of the study. Although the number of patients who were taking daily corticosteroids did not change significantly at 6 months (24% decreasing to 21%), significant reductions in use did occur after 1 year (24% decreasing to 19%, $P = .03$). Perhaps more important, as shown in Table III, mean daily doses of prednisone did decrease significantly at 6 months (10.8 mg/d at baseline decreasing to 8.1 mg/d, $P = .01$) and decreased to 3.6 mg/d during the last year ($P < .0001$). Short courses of systemic corticosteroids decreased significantly at both 6 months (2.7 courses per year at baseline to 0.4 courses for the first 6 months, which is equivalent to 0.8 courses for an entire year; $P < .0001$) and after 1 to 5 years (0.5 courses per year, $P < .0001$).

Individual patient courses are presented in Table V and were calculated at least 1 year or longer after the start of aspirin treatment. Of the 126 patients, 60 (48%) enjoyed an excellent response, with a reduction in all clinical markers for disease activity, as well as doses of nasal and inhaled corticosteroids and systemic corticosteroids; 50 (40%) patients responded clinically, but their doses of topical or systemic corticosteroids remained the same or there were reductions in only 1 or 2 of the following: nasal, inhaled, or systemic corticosteroids. These patients were further subdivided into the following groups: 36 patients experienced reduction in some clinical parameters and improvement in both global assessments but continued to receive the same doses of corticosteroid treatment or had reductions in 1 or 2 of the types of corticosteroids (nasal, inhaled, or systemic), 7 patients experienced improvement in nasosinus parameters and nasosinus global assessment but continued to have the same assessment of asthma with a decrease in nasal corticosteroid treatment only, and 7 experienced improvement in their asthma symptoms, asthma global assessment, and corticosteroid treatment.

As shown in Table V, a group of 16 (12%) of 126 patients failed to respond because of the following clinical courses: 12 patients who had not used prednisone before desensitization required prednisone treatment for worsening asthma (5 patients received short courses of prednisone, and 7 patients changed their use from bursts to daily doses of prednisone), and 4 patients did not experience improvement in their clinical measurements, and their corticosteroid treatment remained the same. With respect to the total number of patients who did not respond to aspirin desensitization therapy, it is appropriate to include 17 of the 22 patients who discontinued aspirin treatment during the first year and the 24 patients who discontinued aspirin treatment because of aspirin-induced gastritis or other aspirin-induced adverse effects. Therefore 57 (33%) of 172 patients discontinued aspirin treatment in the first year (n = 41) or failed to respond to aspirin treatment (n = 16).

Leukotriene modifier therapy

After January 1998, 24 (19%) of 126 patients were taking LTMDs before and at the time of initial evaluation (zafirlukast, 7; montelukast, 13; and zileuton, 4). Of these 24 patients, 19 continued taking the same LTMDs throughout the study. Five patients, classified as excellent responders, discontinued their LTMDs during the first year of the study. Another 5 patients in the post-1998 group, also classified as excellent responders, were not taking LTMDs before or during aspirin desensitization. Only 5 (5%) of 110 responders received add-on LTMDs during the first 6 months, an effect too small to influence statistical results in Tables I and III, which were the same as the results after 1 year. In all, only 25 (22%) of 110 responders received add-on leukotriene receptor antagonists (LTRAs). The remaining patients, after January 1998, took their LTMD treatment both before and throughout the study. A comparison of the patients treated with or without LTMDs might reveal whether response rates to aspirin treatment were influenced by LTMDs. The following responses were compared: no LTMD treatment in 27 excellent responders, 25 good responders, and 6 nonresponders versus LTMD treatment in 23 excellent responders, 25 good responders, and 10 nonresponders ($P = .5$, not significant, Fisher 2-sided exact test). Therefore the responses to aspirin treatment were the same, irrespective of LTMD treatment.

By contrast, 10/10 post-1998 patients who failed to respond to aspirin desensitization because of increased

clinical disease or increased use of systemic corticosteroids were prescribed either zafirlukast or montelukast during or after the first 6 months after aspirin desensitization. In other words, 10/10 patients did not respond to either aspirin desensitization or LTRAs.

DISCUSSION

AERD is an aggressive inflammatory disease of the respiratory mucosa.[11] Most patients with AERD have moderate or severe persistent asthma and are treated in accordance with National Institutes of Health guidelines for management of asthma.[12] However, there are some important differences in the care of patients with AERD. Patients with AERD have nasal polyposis, nasal obstruction, anosmia, and recurrent sinus infections. During the year before baseline evaluation, our study patients experienced an average of 5 bouts of sinusitis per year. During bouts of sinusitis, asthma tends to increase in severity, usually requiring systemic corticosteroids, emergency department visits, and hospitalization for asthma care. Therefore treatment that decreases nasal congestion and sinus infections significantly alters a chain of negative events in patients with AERD.

In some patients with AERD, topical nasal and bronchial inhaled corticosteroids are an effective treatment, and further therapy with systemic corticosteroids or sinus surgery is not necessary.[13] The addition of zileuton[14] or montelukast[15] has also been shown to be an effective treatment for AERD. The predominant effects of LTMDs are directed at the lower bronchial tree, although zileuton has been reported to be beneficial to the upper airways in patients with AERD.[14] Systemic corticosteroids are an effective treatment for inflammatory polypoid upper respiratory tract disease, as well as for asthma.[9] Unfortunately, many patients with AERD have corticosteroid-induced side effects, such as osteoporosis, easy bruising, cataracts, and adrenal suppression. Sinus and nasal polyp operations are effective in removing polypoid nasal and sinus tissues and in opening sinus ostia, but nasal polyps usually return.[16-18]

Several studies have reported that aspirin desensitization, followed by daily aspirin treatment with high doses of aspirin (1300 mg), improved AERD.[7,8] In our prior studies it was pointed out that double-blind placebo-controlled studies of aspirin desensitization treatment could not be conducted because patients immediately observed nasal decongestion at the time of acute aspirin desensitization.[8] Furthermore, 48 to 72 hours after discontinuing aspirin treatment, nasal congestion returned in most patients, thus unblinding any study. In the current study, for the reasons stated above, we did not have a placebo-treated control group. We used objective measurements to analyze the clinical outcomes and added global patient self-assessments at baseline, 6 months of treatment, and the last year of follow-up. For the first time, we showed that improvement in clinical courses, reduction in doses of corticosteroids, and improvement in global assessments occurred as early as 6 months (Tables I and III) and persisted for 1 to 5 years (Tables II and III). In our opinion the reduction in bouts of purulent sinusitis from an average of 5 per year (2.5 to 1.0 by comparing 6 months before with 6 months of aspirin treatment, Table I) is probably the most important change in the clinical course of patients with AERD.

Twenty-four (13%) of 172 patients had to discontinue aspirin desensitization therapy because of side effects. The overwhelming reason for discontinuation of aspirin treatment was gastritis in 16 (66%) of 24 patients (14 with epigastric pain and 2 with hematemesis). In the 1990 study, we reported gastritis in 12 (18.4%) of 65 patients that was severe enough to cause discontinuation of aspirin treatment. In our 1996 study 9 (13.8%) of 65 patients had gastritis and discontinued aspirin treatment. In the current study 16 (9%) of 172 patients discontinued aspirin treatment because of gastritis. It is possible that this decrease in discontinuing aspirin treatment was due to the use of misoprostol and proton pump inhibitors, both of which became available in recent years. For any patients with AERD who had gastric pain during treatment with aspirin, we recommended that doses of aspirin be reduced and the above drugs added to the regimen. In addition, reduction in aspirin treatment doses in the later years of this study might have been prophylactic in allowing more patients to continue aspirin treatment without gastritis.

We determined the clinical outcome of each of the patients (Table V). Our findings demonstrated that 110 (87%) of 126 patients responded to aspirin desensitization treatment. However, as shown in Table V, the actual response rates were probably less because of dropouts in the first year of treatment. The actual response rate, including the 5 patients who probably responded, is more likely to be 115 (78%) of 148 of the patients who did not discontinue aspirin treatment because of side effects from aspirin or 115 (67%) of the starting group of 172 patients. These results suggest that aspirin desensitization treatment is effective add-on therapy in patients with AERD.

During the last 3 years of the study, knowledge about the action of LTMDs made it inevitable that treating physicians would add these drugs in some patients. The important question is whether LTMDs account for the excellent or good responses in the 110 of 126 patients who were classified as responding to aspirin treatment. Although it is impossible to eliminate any therapeutic effect from treatment with LTRAs in the 25 (22%) of 110 responders in whom LTRAs were added by the end of the study, improvement from baseline in the remaining 85 (78%) of 110 responders could not have been due to these drugs.

We tried to determine whether there was any evidence to support the notion that LTMD treatment, instead of aspirin treatment, was responsible for the improvement in the 25 of 110 responders. First, zileuton is the only LTMD that has been shown to have therapeutic effects for improving nasal congestion or restoring smell.[14] Montelukast has only been studied in patients with AERD with respect to its effect on the lower airways.[15] In our current study zileuton (4 patients) was never added after baseline and could not have accounted for the

improvement in clinical courses. In the other patients, in whom LTRAs were added to 14 patients by 6 months and to a total of 40 patients by the end of the study, therapeutic benefits, particularly in the lower airways, might be expected. By contrast, aspirin desensitization appears to have its major effects on the upper airways. In view of the fact that only 5 (5%) of 110 responders received LTRAs as add-on therapy in the first 6 months of aspirin treatment, it is difficult to argue that LTRAs had any significant effect on the statistical differences encountered at 6 months. If LTRAs had no significant effect at 6 months, why would they be responsible for the same improvement at 1 year or longer (Tables I-III)?

In the 58 patients evaluated before 1998 who never took LTMDs, the response rates were the same as in the 58 patients evaluated after 1998 who were taking LTMDs during the last year of the evaluation. If the therapeutic benefits of LTMDs were responsible for the response rates, we should have observed significantly more improvement in the subpopulation that received continuous or add-on treatment with LTMDs. This did not occur. By contrast to the responder groups, the striking 100% prevalence of LTMD prescriptions in the post-1998 patients who failed to respond to aspirin desensitization strongly suggests that physicians added LTMDs because their patients were not responding to aspirin desensitization. Even then, LTMDs did not convert these patients to responders.

We recommend that patients with AERD who do not respond to nasal and inhaled corticosteroids and LTMDs should undergo aspirin desensitization and receive a trial of treatment with daily aspirin as add-on therapy. Patients with aggressive polypoid upper airway disease are prime candidates, with an expected decrease in the need for further polyp-sinus surgery.

Over time, slowly reducing disease-controlling drugs, including aspirin, can be accomplished in some patients. Before this study, we recommended that aspirin doses should be decreased after a year of aspirin treatment in responders or earlier if gastric side effects occur.[7,8] Because of the results of this study, we are now suggesting that doses of aspirin be decreased after 6 months in most AERD responders.

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