

Aspirin 300 mg/day is effective for treating aspirin-exacerbated respiratory disease

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Abstract

Background: Aspirin desensitization (AD) treatment at doses of up to 1300 mg/day improves outcomes in aspirin-exacerbated respiratory disease (AERD). The aim of this study was to investigate the efficacy of aspirin 300 mg/day in the treatment of patients with AERD.

Methods: The study included 40 patients diagnosed in our clinic as AERD that were desensitized and treated with aspirin 300 mg/day between December 2005 and December 2012. Changes from the baseline status were analyzed at 1 year and at 3 years of follow-up.

Results: Of the 40 patients included, 24 (60%) were female and median (interquartile range [IQR]) age was 45 (40–51) years. Median (IQR) duration of AD was 31.5 (10.5–48.5) months. In total, 29 patients continued treatment for at least 1 year and 18 patients for at least 3 years. The annual rate of use of systemic corticosteroid regimens, episodes of sinusitis, and surgery was significantly lower both at 1 year ($P = 0.002$, $P = 0.01$, and $P < 0.001$, respectively) and at 3 years ($P = 0.001$, $P = 0.03$, and $P = 0.002$, respectively). Significant improvement was observed in the nasal congestion score ($P = 0.01$) and sense of smell score ($P = 0.05$) at 1 year and in the postnasal drainage score ($P = 0.01$) at 3 years.

Conclusion: Daily treatment with aspirin 300 mg had beneficial effects in patients with AERD, especially for the control of upper airway disease.

Aspirin-exacerbated respiratory disease (AERD) is a clinical syndrome characterized by nasal polyps, chronic hypertrophic eosinophilic sinusitis, asthma, and sensitivity to cyclooxygenase-1 (COX-1) inhibitors. It affects 0.3–0.9% of the general population, but the prevalence increases to 10–20% in asthmatics and 30–40% in asthmatics with nasal polyposis (1).

Treatment of asthma associated with analgesic intolerance (AI) can be difficult. It was previously reported that 80% of patients with analgesic-induced asthma were treated with relatively high doses of inhaled corticosteroids (800–2000 µg) and 51% required daily oral corticosteroid treatment equivalent to 8 mg of prednisone (2).

Another problem associated with the management of AERD is postsurgical regrowth of nasal polyps. The nasal polyposis recurrence rate ranges between 24% and 80% following different types of surgery (3–6); on average, reoperation for nasal polyps is required every 3 years (7).

Previous studies have shown that aspirin desensitization (AD) treatment successfully reduced upper airway congestion

and nasal polyp formation and improved asthma control in patients with AERD (7–9). AD is recommended for patients with AERD who: (i) have moderate–severe asthma, intractable nasal congestion, or both and have failed to respond to topical corticosteroids, leukotriene receptor antagonists (LTRAs), and 5-lipoxygenase inhibitors; (ii) develop multiple nasal polyps; (iii) require systemic corticosteroids for control of AERD; (iv) require aspirin for other conditions, such as coronary artery disease (10). AD offers a cheap treatment option in patients with AERD, as new and expensive therapies such as anti-IL5 are becoming available (11, 12).

A wide range of aspirin doses (100–1300 mg) have been used for the purpose of AD treatment (8, 9, 13–16) as shown in Table 1; however, there is no consensus on the optimal dose of aspirin necessary to control AERD with a minimum of side effects. This study aimed to investigate the long-term efficacy of aspirin 300 mg/day for the treatment of AERD.

Table 1 Previous studies of effects of aspirin desensitization in patients with AERD

Study	No. patients	ASA dose	Follow-up period	Effects	Side effects (no. patients)
Stevenson (16)	25	325 mg q.d. or 325 mg q.i.d. or 650 mg q.i.d.	7 months (two 3-month-long phases separated by 1 month-long washout period)	Nasal symptoms improved and nasal beclomethasone use reduced during ASA treatment phase, no change in asthma symptoms, FEV1, or antiasthmatic medications. No significant difference between 3 doses of ASA with regard to percentage of patients showing improvement	Gastrointestinal pain:2 Others:3
Sweet (7)	107 (42 control, 35 continuous treatment, 30 discontinued group)	Mean: 650 mg b.i.d. (325 mg q.d–650 mg q.i.d.)	Control group:102 months Continuous treatment group: 46 months Discontinued group:25 months (taking ASA) and 32 months (without ASA)	Improvement in all parameters except nasal steroid use in continuous treatment group. Improvement in all parameters except inhaled and nasal steroid use, but return to baseline after ASA treatment in discontinued group. Higher frequency of improvement in treatment group as compared to controls in all parameters except chest symptoms and nasal steroid use	Gastrointestinal intolerance:12 Others:4
Stevenson (8)	65	325 mg q.d.to 650 mg t.i.d. (mean:1214 mg)	1–6 years (mean:3.1 years)	Reduction in annual numbers of sinus infections, hospitalizations for asthma, sinus, and polyp operations, doses of nasal steroids, use of systemic steroids, improvement in olfaction. Emergency department visits and use of inhaled steroids unchanged	Gastric: 9
Gosepath (13)	30	100 mg q.d.	1 year	Normalization of <i>in vitro</i> eicosanoid levels in 25 of 30 patients, low recurrence rate of nasal polyps (4 of 30), reduction in purulent sinusitis episodes (from 4 to 2), improvement in pulmonary functions in 9 of 12, nasal airflow in 14 of 16, and sense of smell in 7 of 11 patients	–
Berges-Gimeno (9)	172 (126 took aspirin at least 1 year)	Starting dose 650 mg b.i.d. (mean:1138 mg)	1–6 years	Reduction in number of sinus infections, short courses of steroids, doses of nasal, inhaled,	Gastritis (with or w/o bleeding):16 Others: 8

Table 1 (Continued)

Study	No. patients	ASA dose	Follow-up period	Effects	Side effects (no. patients)
				and systemic steroids, improvement in smell, nasal, and asthma symptom scores at 6 months and after 1 year, reduction in annual number of sinus operations, hospitalizations and emergency department visits for asthma after 1 year	
Lee (15)	137	650 mg b.i.d. or 325 mg b.i.d. (1 month), adjustment after 1 month	1 year	Reduction in annual number of sinus infections, sinus polyp operations, hospitalizations for asthma, doses of inhaled and systemic steroids, improvement in nasal sinus, smell, and asthma scores in both groups. No significant change in doses of inhaled steroids	Dyspepsia:12 Others: 14
Rozsasi (14)	39	100 mg q.d. or 300 mg q.d. for 1 year, continued as 300 mg in second part	1–4.5 years (median:2.3 years)	Reduction in nasal polyp recurrence and asthma medications, improvement in nasal patency,sense of smell, and pulmonary functions in 300 mg q.d. group after 1 year. No change in asthma scores in both, and no improvement in other parameters in 100 mg q.d. group after 1 year. Nasal polyposis decreased, asthma, and sinusitis scores improved with 300 mg q.d.aspirin after 2.3 years of median follow-up	Gastrointestinal intolerance:2

AERD, aspirin-exacerbated respiratory disease; ASA, acetylsalicylic acid; FEV1, forced expiratory volume in 1 s.

Material and methods

Participants

The study included 40 patients diagnosed as AERD that underwent AD treatment at our outpatient clinic between December 2005 and December 2012. Patients with asthma and chronic rhinosinusitis – with or without nasal polyposis – and confirmed AI were included in the study. Chronic rhinosinusitis was diagnosed according to the general guidelines (17), by nasal endoscopy and/or computer

tomography, which were performed in all and in 26 patients, respectively. Aspirin sensitivity was diagnosed based on single-blind oral aspirin provocation testing, which was performed in all the patients according to accepted guidelines (18). Tests were considered positive if there was a 20% fall from baseline in the forced expiratory volume in 1 s (FEV1) and/or profound naso-ocular reactions. The local ethics committee of Hacettepe University approved the study protocol, and written informed consent was provided by each participant.

Aspirin desensitization and follow-up

Aspirin desensitization was performed beginning with a dose of 25 mg and sequentially increasing the dose as 50, 75, 100, and 250 mg 90 min apart from each other until the patient experienced a clinical reaction. In Turkey, aspirin is commercially available in 100-, 300-, and 500-mg tablets. These doses were achieved by splitting the aspirin tablets. The procedure was carried out on an outpatient basis, but under close medical supervision. The patients had to be clinically stable with a basal FEV1 value of no lower than 70% of predicted. An intravenous line was placed before starting the procedure. Blood pressure, pulse rate, and peak expiratory flow were measured at baseline and every 30 min during the procedure. If any clinical symptoms (bronchial and/or naso-ocular) occurred, AD was promptly stopped, and the patient was evaluated and treated as necessary. The same reacting dose was repeated on the same day if the reaction resolved within 3 h, otherwise on the next morning. All patients in the study had reactions of some degree of bronchospasm and/or rhinoconjunctivitis, but all these reactions were treated on the same day in our outpatient clinic, and no hospitalizations were necessary. On the second day of AD procedure, all patients were able to take overall 500 mg of aspirin and continued to take 300 mg aspirin orally at home on the following days, which was a lower dose than used in some previous AD treatment trials (7–9); this dose was selected to avoid the gastrointestinal side effects observed at higher doses.

Baseline demographic and clinical characteristics, including age, gender, duration of asthma, rhinosinusitis, AI, and the number and dates of sinus surgery and/or polypectomy; and medical treatments for asthma and rhinosinusitis were also recorded. The number of hospital admissions, emergency department visits, short courses of oral corticosteroid treatment, and episodes of sinusitis that required antibiotic treatment during the year prior to the study entry were collected. Patients scored their sinonasal and respiratory symptoms (nasal congestion, rhinorrhea, postnasal drainage, sense of smell, snoring, wheezing, dyspnea, and cough) as follows: 1: very bad; 2: bad; 3: fair; 4: good; 5: very good. Quality of life was measured using the Short Form-36 (SF-36) questionnaire (19). Spirometric measurement was performed according to the standardized methods (20), and percentage of peripheral blood eosinophils was obtained. All patients came for follow-up visits and were evaluated for all of these parameters every 3 months.

All patients were followed up via endoscopic examination by the same two experienced otorhinolaryngologists, and any need for surgical treatment was assessed at baseline and at follow-up visits every 3 months. Using endoscopy, polyp size was scored from 0 to 3 for each nasal cavity as follows: 0: no polyps; 1: mild polyposis (small polyps not reaching the upper edge of the inferior turbinate); 2: moderate polyposis (polyps between the upper and lower edges of the inferior turbinate); and 3: severe polyposis (large polyps reaching the lower edge of the inferior turbinate) (21). If a patient had sinonasal polyposis that required surgical treatment (stage 2 or above polyps) at study entry, they first underwent surgery,

and AD treatment was started 3–6 weeks postsurgery. As there are no widely accepted and standard criteria for reoperation in patients with AERD already receiving AD treatment, in our study, further surgery was offered to the patients by the otorhinolaryngologists when a significant worsening of clinical symptoms especially nasal congestion occurred together with the observation of stage 2 or above polyps on endoscopic examination. All surgeries were performed as functional endoscopic sinus surgery (FESS) by the same two otorhinolaryngologists.

Patients were medically treated in a similar fashion before and after AD, which was in accordance with international guidelines for the management of asthma and rhinitis (17, 22, 23).

Statistical analysis

Descriptive statistics are expressed as median and interquartile range (IQR) for continuous variables, and number and percentage for categorical variables. Changes from baseline values were evaluated after 1 year and after 3 years of treatment. The Wilcoxon signed-rank test was used to compare two continuous variables, and the McNemar test was used to compare two categorical variables. FEV1%, symptom and SF-36 questionnaire scores, and asthma/rhinitis treatments at 1 year and 3 years were compared with baseline. Inhaled corticosteroid doses were calculated as budesonide equivalents. Change in the annual rate of use of systemic corticosteroid regimens, episodes of sinusitis, emergency department visits, and hospitalizations for asthma was based on a comparison of the number of events during 1 year of AD treatment and the number of events during the year prior to the study entry. Change in the number of surgeries was based on the comparison of the number of surgeries during 1 year of AD treatment and the number of surgeries divided by the number of years the patient had chronic rhinosinusitis prior to the study. The Kruskal–Wallis test was used to compare three groups with different follow-up data (<1 year, 1–3 years, and >3 years). *P* values <0.05 was considered statistically significant.

Results

Median age of the study group (*n* = 40) was 45 (40–51) years and 60% were female. Median duration of asthma, rhinitis, and analgesic intolerance was 13.5 (7–19) years, 13 (8.25–17.75) years, and 12 (8–17) years, respectively. The median number of previous polypectomies and/or sinus surgeries was 2.5 (1.25–3), and median duration of AD treatment was 31.5 (10.5–48.5) months.

During the 7-year study period, 11 patients were lost to follow-up and seven discontinued AD treatment. Reasons for discontinuation of AD treatment were as follows: gastric side effects (*n* = 3), pregnancy (*n* = 1), no benefit from treatment (*n* = 2), and ecchymosis (*n* = 1). In all, 11 patients were followed up <1 year and were not included in the statistical analyses. At the end of 1 year and 3 years, 29 patients and 18 patients, respectively, were still continuing the AD treatment, and treatment outcome was assessed at the two time-points. The patients that were followed up <1 year, 1–

3 years, and >3 years had similar baseline clinical characteristics (Table 2).

In the subgroup of 29 patients that received AD treatment for at least 1 year, there were significant reductions in the annual rate of use of systemic corticosteroid regimens and episodes of sinusitis ($P = 0.002$ and $P = 0.01$, respectively). The annual rate of sinus surgery also decreased significantly at 1 year ($P < 0.001$). The median time interval between the last prestudy surgery and start of AD treatment was three (2–16) months. Only one patient required sinus surgery during the seventh month of AD treatment; this patient had not previously undergone sinus surgery and had stage 2 polyps at baseline, but had refused to undergo surgery prior to study entry. FEV1%, percentage of peripheral blood eosinophils, and number of emergency department visits and hospitalizations for asthma, medical asthma, and rhinitis medications remained unchanged. At baseline, there were two patients requiring regular systemic steroid treatment for severe persistent asthma, who could not discontinue their treatment at the end of 1 year (Table 3). Nasal congestion and sense of smell scores improved significantly at 1 year ($P = 0.01$ and $P = 0.05$, respectively), whereas other symptom scores did

not show any significant change. The SF-36 general health domain score also improved significantly ($P = 0.001$) (Table 4).

When the subgroup of 18 patients that received AD treatment for ≥ 3 years were analyzed, improvement in the annual rates of use of systemic corticosteroid regimens, episodes of sinusitis, and surgery persisted ($P = 0.001$, $P = 0.03$, and $P = 0.002$, respectively). Median time interval between the last surgery and beginning of AD treatment was 2.5 (2.0–8.25) months. During 3 years of AD treatment, there was a need for surgical treatment in 2 patients – during the 2nd and 3rd years of treatment (one each). At the time of the beginning of AD treatment, these patients had stage 1–2 and stage 2–3 polyps, respectively. FEV1%, percentage of peripheral blood eosinophils, emergency department visits, and hospitalizations for asthma, medical asthma, and rhinitis medications remained unchanged from baseline at 3 years (Table 5). The postnasal drainage score significantly improved at 3 years ($P = 0.01$), whereas the previous improvement in the nasal congestion score lost its significance. The sense of smell score also improved at 3 years; however, this improvement did not reach statistical

Table 2 Patient characteristics according to follow-up data

	All patients (<i>n</i> = 40)	Follow-up <1 year (<i>n</i> = 11)	Follow-up of 1–3 years (<i>n</i> = 11)	Follow-up >3 years (<i>n</i> = 18)	<i>P</i>
Age*	45 (40–51)	50 (38.5–53)	43 (40–51.25)	45 (37.5–51.25)	0.91
Females (%)	24 (60)	6 (54.5)	6 (54.5)	12 (66.7)	0.74
Asthma (years)*	13.5 (7–19)	8 (7–28)	11.5 (5–15.25)	17.5 (11.75–21)	0.24
Analgesic intolerance (years)*	12 (8–17)	6 (4.5–15.5)	9.5 (7.5–12.25)	15.5 (11–19.5)	0.02
Rhinitis (years)*	13 (8.25–17.75)	14 (6–19)	8.5 (7.5–11.5)	13.5 (11.5–21)	0.14
Number of past surgeries*	2.5 (1.25–3)	3 (1–5.5)	2 (1.75–3)	2.5 (1.75–3.25)	0.93
Baseline FEV1%*	83 (72–93)	75 (68–85)	83.5 (66.5–88.25)	90 (78.75–104)	0.07

*Values are expressed as median and interquartile range.

Statistically significant values $P < 0.05$ are shown in bold.

Table 3 Comparison of clinical parameters at baseline and 1 year (*n* = 29)

	Baseline	1 year	<i>P</i>
FEV1%*	84.00 (72.50–94.00)	80.00 (72.00–95.50)	0.13
Eosinophil%*	5.7 (2.7–10.05)	6.70 (3.00–9.85)	0.43
Systemic corticosteroid regimens/year*	2.00 (1.00–3.00)	0.50 (0–1.75)	0.002
Sinusitis episodes/year*	1.00 (0–3.75)	0 (0–1.00)	0.01
Emergency department visits/year*	0 (0–1.00)	0 (0–0)	0.35
Hospitalizations for asthma/year*	0 (0–0)	0 (0–0)	0.56
Surgeries/year*	0.21 (0.15–0.28)	0 (0–0)	<0.001
Regular systemic corticosteroid use, <i>n</i> (%)	2 (6.9)	2 (6.9)	1.00

*Values are expressed as median and interquartile range.

Statistically significant values $P < 0.05$ are shown in bold.

Table 4 Comparison of symptom scores and SF-36 domain scores at baseline and 1 year ($n = 29$)

	Baseline	1 year	<i>P</i>
Median symptom scores (IQR)			
Nasal congestion	3.00 (3.00–4.00)	4.00 (3.00–4.00)	0.01
Rhinorrhea	3.50 (2.00–4.00)	3.50 (3.00–4.00)	0.51
Postnasal drainage	3.00 (2.25–4.00)	3.00 (2.25–4.00)	0.22
Sense of smell	1.00 (1.00–2.75)	2.00 (1.00–3.00)	0.05
Snoring	4.00 (3.00–4.75)	4.00 (3.00–5.00)	0.66
Wheezing	4.00 (3.00–4.00)	4.00 (3.00–4.00)	0.92
Dyspnea	4.00 (3.00–4.00)	4.00 (3.00–4.00)	0.44
Cough	4.00 (4.00–5.00)	4.00 (4.00–4.75)	0.72
Median SF-36 questionnaire scores (IQR)			
Physical function	77.50 (65.00–85.00)	72.50 (55.00–88.75)	0.28
Role-physical	75.00 (6.25–100.00)	75.00 (0–100.00)	0.86
Bodily pain	72.00 (51.00–84.00)	62.00 (41.00–100.00)	0.84
General health	42.00 (25.00–50.00)	48.50 (35.50–72.00)	0.001
Vitality	57.50 (40.00–73.75)	55.00 (45.00–75.00)	0.61
Social functioning	75.00 (62.50–96.87)	75.00 (50.00–100.00)	0.61
Role-emotional	100.00 (66.70–100.00)	66.70 (0–100.00)	0.05
Mental health	64.00 (52.00–80.00)	68.00 (52.00–84.00)	0.88
Sum of physical function	43.10 (34.30–49.70)	47.50 (36.30–52.30)	0.41
Sum of mental health	48.60 (43.70–54.80)	43.30 (36.30–56.10)	0.24

Statistically significant values $P < 0.05$ are shown in bold.

Table 5 Comparison of clinical parameters at baseline and 3 years ($n = 18$)

	Baseline	3 year	<i>P</i>
FEV1%*	90.00 (78.75–104.00)	87.50 (79.50–95.75)	0.23
Eosinophil%*	4.70 (2.50–11.72)	6.90 (4.12–13.50)	0.17
Systemic corticosteroid regimens/year*	2.00 (1.00–3.00)	0.33 (0–0.83)	0.001
Sinusitis episodes/year*	1.00 (0–3.50)	0.33 (0–1.16)	0.03
Emergency department visits/year*	0 (0–1.00)	0 (0–0)	0.09
Hospitalizations for asthma/year*	0 (0–0)	0 (0–0)	0.27
Surgeries/year*	0.18 (0.13–0.26)	0 (0–0)	0.002
Regular systemic corticosteroid use, n (%)	0	0	n/a

*Values are expressed as median and interquartile range.

Statistically significant values $P < 0.05$ are shown in bold.

significance. The SF-36 general health domain score also improved significantly at 3 years ($P = 0.02$) (Table 6).

Discussion

In the present study, the annual rates of use of systemic corticosteroid regimens, episodes of sinusitis, and surgery in patients with AERD significantly decreased both at 1 year and at 3 years of treatment with aspirin 300 mg/day. Significant improvement was also observed in the nasal congestion and sense of smell scores at 1 year and the postnasal drainage score at 3 years.

The major goals of the control of AERD are prevention of nasal polyp formation, secondary sinusitis, and exacerbation of asthma using treatment strategies that target reducing inflammation in both the upper and the lower airways. High doses of topical corticosteroids (nasal/inhaled) are usually needed for such treatment; however, inflammation in some

patients with AERD cannot be controlled by topical corticosteroids alone, and frequent bursts or continuous treatment with systemic corticosteroids is required (24). In the present study, short courses of systemic corticosteroids were required twice a year on average, despite regular treatment with moderate to high doses of inhaled and nasal corticosteroids at the beginning of the study.

Aspirin desensitization followed by daily aspirin is an effective treatment option for patients with AERD that have not benefited from conventional therapy, especially those patients with recurrent nasal polyps and those dependent on systemic corticosteroids (10). In the present study, the median number of previous surgeries was 2.5 in a median rhinosinusitis duration of 13 years. There were two patients dependent on systemic corticosteroids, both of which had severe persistent asthma.

Many studies have shown that AD followed by daily aspirin treatment was associated with an improved clinical course

Table 6 Comparison of symptom scores and SF-36 domain scores at baseline and 3 years ($n = 18$)

	Baseline	3 year	<i>P</i>
Median symptom scores (IQR)			
Nasal congestion	3.00 (2.00–4.00)	4.00 (3.00–4.00)	0.13
Rhinorrhea	3.00 (2.00–4.00)	4.00 (3.00–4.00)	0.17
Postnasal drainage	3.00 (2.50–4.00)	4.00 (3.00–4.00)	0.01
Sense of smell	1.00 (1.00–3.00)	3.00 (1.00–4.00)	0.06
Snoring	4.00 (2.00–4.50)	4.00 (3.00–4.50)	0.34
Wheezing	4.00 (3.00–4.00)	4.00 (3.00–4.00)	0.52
Dyspnea	4.00 (3.00–4.00)	4.00 (3.00–4.00)	0.42
Cough	4.00 (4.00–5.00)	4.00 (3.00–5.00)	0.34
Median SF-36 questionnaire scores (IQR)			
Physical function	85.00 (67.50–87.50)	85.00 (72.50–92.50)	0.54
Role-physical	75.00 (12.50–100.00)	100.00 (62.50–100.00)	0.07
Bodily pain	74.00 (51.50–92.00)	72.00 (56.50–84.00)	0.39
General health	38.50 (25.00–50.75)	57.00 (40.00–67.00)	0.02
Vitality	55.00 (40.00–70.00)	60.00 (52.50–75.00)	0.49
Social functioning	75.00 (62.50–93.75)	75.00 (62.50–100.00)	0.52
Role-emotional	100.00 (66.70–100.00)	100.00 (50.00–100.00)	0.83
Mental health	64.00 (52.00–74.00)	68.00 (54.00–84.00)	0.21
Sum of physical function	42.80 (36.92–51.75)	49.30 (45.75–52.65)	0.08
Sum of mental health	48.05 (43.82–52.62)	50.40 (37.30–57.10)	0.94

Statistically significant values $P < 0.05$ are shown in bold.

in patients with AERD (7–9, 16); particularly, good responses have been noted in the upper airways. In a short-term, double-blind crossover study (16), AD treatment of patients with combined rhinosinusitis/asthma was associated with significant improvement in upper airway symptoms, but not in lower airway symptoms. The researchers suggested that sphenoidectomy followed by AD and daily aspirin treatment should constitute the standard treatment for patients with aspirin-sensitive rhinosinusitis/asthma; however, they also reported that even after this combined treatment approach, the asthmatic symptoms and airway function may not significantly improve because of the presence of other asthmogenic pathways unaffected by sinobronchial reflexes or aspirin. Other studies support this hypothesis. A long-term study (7) reported that the aspirin treatment group had a significantly higher frequency of improvement (as compared to the control group) in all clinical parameters, except for chest symptoms and nasal steroid use. In another study (8), 65 patients were treated with a mean daily aspirin dose of 1214 mg for a mean duration of 3.1 years. The researchers noted that there were significant reductions in the number of episodes of sinusitis and hospitalizations, daily prednisone dose, sinus and polyp surgery, and nasal corticosteroid dose; however, emergency department visits for asthma and the dose of inhaled corticosteroids did not decrease significantly. In the present study, better responses to AD were observed in the upper airway than in the lower airway.

Aspirin doses ranging from 100 to 1300 mg/day were reported to be effective for the treatment of AERD (8, 9, 13–16). One study (15) reported that aspirin dosages of 325 and 650 mg b.i.d. were both similarly associated with significant improvement in the clinical markers of disease at the end of 1-year follow-up period. The researchers suggested

that daily aspirin treatment should be started at a dose of 650 mg b.i.d. and after 1 month should be decreased to the lowest effective dosage (usually 325 mg b.i.d.) if there is symptomatic improvement.

A recent study by Rozsasi et al. (14), which consisted of two parts, showed that 300 mg/day aspirin was effective in preventing polyp recurrences and improving nasal patency and the sense of smell score at the end of a follow-up period of 1 year. In the second part of that study, no patients out of the 35 taking 300 mg/day AD treatment required revision surgery in a median follow-up period of 2.3 years. In our study, one patient and two patients in the groups with follow-up periods of at least 1 year and at least 3 years required surgery, respectively, but these patients already had stage 2 or higher-stage polyps at baseline and had refused to undergo surgery before study entry, which may indicate a progression rather than a recurrence of polyps. The improvements in nasal congestion and the sense of smell scores at the end of 1 year in our study were similar to the findings of the study by Rozsasi et al.

The asthma scores did not show significant change with 300 mg/day AD treatment at the end of 1 year in the study by Rozsasi et al., which was similar to our findings. However, there was an improvement in the pulmonary function tests, the ability to reduce asthma medications at the end of 1 year, and the asthma scores after a median follow-up period of 2.3 years in that study, which were not observed in our study. One explanation for this discrepancy may be the different patient characteristics in their group and our group. In our study, only 2 of 40 patients were taking regular systemic steroids at baseline. This number was higher in the study by Rozsasi et al. (three of seven patients in the first and 22 of 36 patients in the second part were taking systemic steroids), which may reflect a heavier baseline disease status

in their group and may help to explain why they benefitted more from AD treatment in terms of pulmonary functions and reduction in asthma medications.

The present study aimed to evaluate the effectiveness of aspirin 300 mg/day and to avoid the potential adverse effects associated with higher doses; only three patients discontinued AD due to gastric side effects. This rate was lower than the rates reported in previous studies, where AD treatment was performed at mean aspirin doses of 1300 and 1214 mg/day (7, 8).

In addition to oral AD treatment, there are also clinical trials evaluating the efficacy of intranasal lysine-aspirin (LAS) therapy. In a long-term, prospective, controlled study (25), treatment with LAS after surgical polypectomy led to a significant reduction in recurrence rate of polyps at 1st, 3rd, and 6th year of follow-up as compared to controls without any adverse effects. The authors concluded that the observed effect was due to nonspecific anti-inflammatory properties of LAS rather than to desensitization, as LAS was highly effective in both aspirin-tolerant and aspirin-sensitive patients. There were other studies confirming the anti-inflammatory properties of LAS (26, 27).

In the present study, patients with extensive sinonasal polypoid disease underwent surgery prior to starting AD treatment. All of these surgical procedures were performed as FESS rather than polypectomies at the otorhinolaryngology department of our hospital. As most AI patients suffer from diffuse polypoid growth, polypectomy alone should be avoided, as the effects are short-lived (28). The findings of previous studies indicate that debulking sinus polypoid tissue in appropriately selected patients before AD is a better strategy than waiting for the slower reduction in nasal tissue inflammation after beginning AD (8). It is suggested that AD treatment should be started 3–6 weeks postsurgery, because polypoid mucosal changes tend to reoccur early in patients with AERD (29). We think that AD followed by FESS – when necessary – is associated with good clinical outcomes and a reduced need for surgery for up to 3 years.

There are some limitations of this study. First, ideally, a randomized, double-blind, and placebo-controlled design should have been used, but such a design is not feasible for AD trials in patients with AERD for reasons detailed elsewhere (7). Blinding aspirin treatment is hampered primarily by ethical reasons. An open AD treatment option should be offered to patients completing an aspirin challenge/desensitization procedure. Additionally, the patients have to be informed and written consents taken before starting desensitization. Although a comparison with a placebo-treated control group could not be performed, we identified 89 patients with AERD who never received AD treatment from the clinical records kept in our clinic since 1991. The median (IQR) annual rate of sinonasal surgery in those patients was 0.30 (0.06–1.00) (unpublished data), in parallel with the general knowledge that reoperation for nasal polyps is required every 3 years. This number was greater than the annual number of surgeries in patients receiving AD treatment both at 1 year and 3 years of follow-up in

our study, which may help refuting the possibility that the change in the annual rate of sinonasal surgeries seen in our study relates simply to chance and not to aspirin. Second, an objective upper airway measurement such as nasal inspiratory peak flow, rhinomanometry, acoustic rhinometry, or threshold test for olfaction could have been used in the follow-up of patients. However, according to the results of previous studies, the subjective sensation of nasal obstruction and rhinomanometric or nasal peak flow evaluations show good intra-individual correlations (30–32). Subjective evaluation of the sense of smell is correlated with the objective olfactory threshold test and the qualitative tests of olfaction (33, 34). Furthermore, the evaluation for the symptom scores was repeated every 3 months, which may decrease the possibility of a biased result when the measurements are taken on a single occasion at a certain time-point. Nasal endoscopic examination, which was also performed every 3 months in the follow-up of patients and primarily used for the decision of reoperation requirement, helped to provide an objective evaluation of the upper airways. Third, there could be an attempt to verify compliance of the patients to aspirin therapy. However, as the patients with AERD usually suffer from severe disease, nonadherence to treatment may be a less important problem in them compared with other asthmatics. For our group, all patients were very willing to participate in the study and take AD treatment with an expectation of better disease control and reduced need for surgery.

In conclusion, AD treatment with 300 mg/day following FESS – when necessary – is an effective treatment option for controlling AERD, particularly for reducing the severity of upper airway symptoms and the need for sinus surgery. Patients with AERD that require frequent surgery for recurrent sinonasal polypoidosis are good candidates for this treatment.

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Author contributions

Sule Comert made the literature search and data analysis and wrote the article. Ebru Celebioglu and Tuba Erdogan contributed to the data collection. Taskin Yucel and Metin Onerci performed otorhinolaryngologic examinations and sinonasal operations. Gul Karakaya contributed to the discussion and writing of the whole article. Ali Fuat Kalyoncu supervised the whole study design and article writing and made the necessary corrections to the article.

Conflict of interest

The authors declare that there are no conflicts of interest.

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