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Original Article

Regular Treatment With Aspirin 300 mg/day After Desensitization in Patients With N-ERD: 12-Year Results

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Abstract

OBJECTIVE: Aspirin desensitization is recommended for patients with nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity, in whom asthma is uncontrolled despite medical treatment, and/or frequent endoscopic sinus surgery (ESS) is required due to nasal polyps. There are few studies in the literature on long-term follow-up of patients undergoing regular aspirin treatment after desensitization. This study aims to evaluate the effect of regular aspirin treatment on respiratory function, symptom control, quality of life, and the number of nasal surgeries required during a period of 12 years.

MATERIAL AND METHODS: A total of 18 patients were included in the study in 2006; 11 patients were excluded and 7 patients regularly taking aspirin for 12 years were evaluated. Oral aspirin desensitization was performed at 4-6 weeks following the ESS. Patients receiving 300 mg/day aspirin were followed up in control visits every 3 months. Nasal and respiratory system examinations and pulmonary function test were performed, and all patients responded to the SF-36 Quality of Life scale during each visit.

RESULTS: There was no change in respiratory function parameters following the12-year aspirin treatment. There was no statistically significant improvement in the quality of life; however, the need for ESS due to the recurrence of nasal polyps decreased significantly (P = .000). At the 12-year follow-up, all symptom scores improved, but improvement in the postnasal drip score was statistically significant (P = .046).

CONCLUSION: Long-term regular treatment with aspirin at a dose of 300 mg/day in patients with N-ERD improved symptom scores, and alleviated the need for ESS due to nasal polyp recurrence.

KEYWORDS: Aspirin desensitization, asthma, endoscopic sinus surgery, nasal polyp, NSAID hypersensitivity
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INTRODUCTION

The relation between aspirin sensitivity, asthma, and nasal polyps was first described by Widal et al.[1] in 1922. Aspirin sensitivity was redefined as aspirin triad by Samter and Beers in 1960.[1] Jenkins et al.[2] showed that other nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen, and diclofenac, also caused reactions in asthmatic patients with aspirin sensitivity.[2]

Aspirin-exacerbated respiratory disease is currently named as NSAIDs-exacerbated respiratory disease (N-ERD).[3] The incidence of N-ERD based on the patient's history in a study conducted by Vargese et al.[4] was 2% and 2.7% in children and adult asthmatic patients, respectively. When drug provocation tests were performed, the incidence of N-ERD increased to 21% and 5% in adult and pediatric asthmatic patients, respectively.

In the present study, severe asthmatic patients with N-ERD were treated with 300 mg/day aspirin after desensitization when their asthma symptoms were uncontrolled under an optimal treatment regime, and/or they had recurrent nasal polyposis after the endoscopic sinus surgery (ESS). After the initiation of the treatment, patients were followed-up in scheduled control visits. In the literature, there are few studies on the long-term follow-up of patients receiving regular aspirin treatment after desensitization (ATAD), and in these studies, an aspirin dose of 600 mg/day or higher was administered during treatment.[5-7] The present study aims to evaluate the effect of a 300 mg/day dose of aspirin during a 12-year period, on respiratory function, symptom control, quality of life, and the number of nasal surgeries required in patients with N-ERD.

MATERIAL AND METHODS

A total of 18 patients who were administered regular ATAD in 2006 were included in the study. During the 12-year follow-up, 3 patients had to discontinue the treatment due to various reasons (eosinophilic granulomatous polyangiitis (EGPA) (n = 2), recurrent angioedema (n = 1)), and 8 patients were lost to follow-up because they did not come for the control visit. Seven patients who received regular aspirin for 12 years were evaluated. Oral aspirin desensitization was

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Table 1. The General Characteristics of the Patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age (years)	66	58	57	50	54	43	66
Gender	m	m	f	m	m	f	f
Age of symptom onset (years)	30	26	32	23	21	20	35
Severity of asthma (GINA 2020)	Step 5	Step 5	Step 4	Step 4	Step 4	Step 5	Step 5
Baseline FEV1 (%)	70	78	105	103	95	74	81
At the 12-year follow-up mean FEV1 (%)	80	73	97	87	88	72	81
Baseline FEF25-75 (%)	40	44	80	62	66	54	68
Mean FEF25-75 (%) at the 12-year follow-up	42	42	82	60	64	50	70
Number of ESS before ATAD	3	5	2	5	7	5	5
Number of ESS after ATAD	0	0	0	2	1	1	1

m, male; f, female.

performed 4 to 6 weeks following ESS. Aspirin provocation tests were not performed if the patients had at least 2 respiratory symptoms within 6 hours after the administration of 2 different NSAIDs.

Aspirin is available in 100, 300, and 500 mg tablets in Turkey. Desensitization was started with a 25 mg aspirin tablet, followed by escalated doses of 50, 100, 150, and 300 mg, administered at 30- to 60-minute intervals in our outpatient clinic. Physical examination, peak flow meter measurements, and evaluation of respiratory, nasal, and ocular symptoms, were performed after the administration of each dose regimen. If nasal, ocular, or pulmonary symptoms occurred, desensitization was immediately stopped and the patient was evaluated and treated as necessary. When the reaction resolved within 3 hours, the same reaction dose was repeated on the same day. If the reaction did not resolve, the same reaction dose was repeated the next day. The target cumulative dose for aspirin was 625 mg. Patients who reached the target dose of 625 mg were considered eligible for the long-term maintenance treatment. Aspirin desensitization was not performed in patients with bleeding disorders, peptic ulcer, pregnancy, or psychiatric disorders, and if FEV1 before the desensitization was less than 70% of the predicted value.

MAIN POINTS

- Aspirin desensitization is recommended for patients with nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity, in whom asthma is uncontrolled despite medical treatment, and/or frequent endoscopic sinus surgery (ESS) is required due to nasal polyps.
- Regular treatment with aspirin at 300 mg/day after desensitization as a daily dose in patients with N-ERD improves symptom scores, and alleviates the need for ESS due to nasal polyp recurrence in the long term.
- There were no reported side effects related to the intake of aspirin.

After the aspirin desensitization procedure, patients continued to use aspirin at a dose of 300 mg/day. Patients who were treated with the 300 mg/day dose were followed-up in control visits every 3 months. Nasal and respiratory system examinations, the SF-36 Quality of Life scale, symptom score evaluation, complete blood count, and pulmonary function test were performed on patients in each visit. Patients responded to a visual analog scale with a 5-point Likert-type design numbered from 1 to 5, 1 indicating severe and 5 indicating no problem, for the complaints of nasal congestion, rhinitis, postnasal drip, smelling, snoring, wheezing, coughing, and dyspnea in each visit. Any side effects were recorded, and treatment modifications were made based on asthma control level. Patients were examined by an ENT specialist at least once a year or in case of significant nasal symptoms.

All participants were informed about the nature of the study, and a written informed consent was obtained. The study protocol was approved by the Hacettepe University Faculty of Medicine Ethics Committee (No. GO 19-206). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was performed using the SPSS Version 20.0 software (IBM SPSS Corp.; Armonk, NY, USA). Descriptive data and the frequency distributions for categorical variables were expressed in mean ± standard deviation. The relationship between categorical variables was evaluated using the Wilcoxon signed-rank test, the Student's *t*-test, and marginal homogeneity tests. A *P* value of $<.05$ was considered statistically significant.

RESULTS

After the exclusion of 11 patients, 7 patients (3 male and 4 female) who were on regular ATAD between 2006 and 2018 were evaluated. The mean age of patients was 56.1 ± 8.2 years (min 43; max 66). The general characteristics of

Table 2. Comparison of Pulmonary Function Tests of the Patients at Baseline and 12th Year

	Baseline (mean ± SD)	At the 12-year follow-up (mean ± SD)	*P*
FEV1 (%)	86.5 ± 14.2	82.5 ± 8.8	.23
FEV1 (ml)	3000 ± 786	2822 ± 572	.29
FEV1/FVC (%)	72.5 ± 9.8	70.2 ± 11.4	.28
FEF25-75 (%)	59.1 ± 14.1	58.5 ± 14.9	.56

SD, standard deviation.

Table 3. Comparison of Symptom Scores of the Patients

	Baseline	At the 12-year follow-up	*P*
Nasal congestion	2.28 (bad-moderate)	3.3 (moderate-mild)	.071
Rhinitis	2.7 (bad-moderate)	3.4 (moderate-mild)	.059
Postnasal drip	2.28 (bad-moderate)	3.4 (moderate-mild)	**.046**
Snoring	2.8 (bad-moderate)	3.2 (moderate-mild)	.25
Wheezing	4.0 (mild)	4.0 (mild)	1.00
Cough	3.7 (moderate-mild)	4.2 (mild-not a problem)	.15
Dyspnea	3.7 (moderate-mild)	4.0 (mild)	.41
Smell	1.86 (severe-bad)	2.1 (bad-moderate)	.41

1 = severe, 2 = bad, 3 = moderate, 4 = mild, 5 = no problem. A statistical significance of $P < .05$ is highlighted in bold.

the patients are shown in Table 1. The mean FEV1 value was 3000 mL (86.5%) before aspirin treatment (min 1670 mL; max 4220 mL). There was no change in respiratory function parameters at the end of 12-year period of ATAD (Table 2). At the 12-year follow-up, all the symptom scores improved but not in statistical significance; however, there was a statistically significant improvement in the postnasal drip score ($P = .046$) (Table 3).

The SF-36 Quality of Life Scale was applied to the patients before the desensitization and in each visit during the follow-up. There was no statistically significant improvement in the quality of life (Table 4). Aspirin treatment was interrupted in 6 of these 7 patients due to various surgical procedures (7 surgical procedures were performed, and 5 of them were ESS). The patients were desensitized with aspirin once again after the surgery. There were no side effects reported related to the intake of aspirin. Before aspirin treatment, the total number of ESS procedures was 32, and this was down to 5 during the 12 years of ATAD ($P = .000$).

Table 4. SF-36* Scale Results at Baseline and 12th Year Follow-up

	Baseline	At the 12-year follow-up	*P*
Physical functioning	77.1 ± 11.8	81.6 ± 22.1	.35
Physical role functioning	57.1 ± 40.3	66.4 ± 32.4	.46
Emotional role functioning	66.7 ± 34	82.3 ± 14	.07
Vitality	46.5 ± 24.7	54.9 ± 25.4	.34
Mental health	58.3 ± 26.8	66.8 ± 17.7	.17
Social role functioning	60.7 ± 27.4	73.5 ± 22.6	.07
Pain	75.3 ± 22.2	80.9 ± 14.4	.16
General health perceptions	38.8 ± 19.2	53.6 ± 17.4	.07

*SF-36 assesses health status. The scores of the subscales range from 0 to 100, with a high score indicating good health. It is not possible to calculate the total score of the scale.

DISCUSSION

The present study results showed that in the long term, almost half of the patients with N-ERD who were scheduled to receive regular ATAD were lost to follow-up (44%). However, the regular use of aspirin was effective in alleviating the need for nasal surgeries in the remaining patients. In the literature, there is no other long-term study evaluating the use of 300 mg regular ATAD, and the results of the study are significant. As the reported incidence of adverse symptoms related to aspirin intake was as high as 34%, dose reduction and recommendation of the lowest effective dose should be considered.[8] In the current study, there were no reported side effects related to the intake of aspirin.

Desensitization induces a temporary state of clinical tolerance. Maintaining the desensitized state depends on the continuous presence of the drug in the patient's circulatory system. If the drug is discontinued, the desensitized state will disappear shortly after the medication is cleared from the bloodstream.[8] The optimal dose for desensitization is unknown, and different desensitization protocols and doses are administered in different clinics. The dose range for aspirin desensitization is quite wide and it ranges from 100 to 1300 mg in the literature.[7-12] In a study, at the end of a 1-year follow-up period, aspirin doses of 325 and 650 mg q.d. were both similarly associated with significant improvement in the

clinical markers of the disease.[12] Another study showed that an aspirin dose of 300 mg/day was effective in preventing polyp recurrences and improving the sense of smell score at the end of a 1-year follow-up period. In the latter study, asthma scores did not show significant change with 100 mg/day aspirin, and in these patients taking 100 mg aspirin, recurrent nasal polyps were also observed.[11] Several studies showed that high doses were beneficial; however, gastrointestinal side effects were more common with high doses.[13,14] In a study conducted by Comert et al.[15] in our clinic, 40 patients diagnosed with N-ERD who were desensitized were included and treated with aspirin at 300 mg/day. The changes in values from the baseline were analyzed at the end of the first and third years. This study showed that treatment with 300 mg/day following ESS was an effective treatment option to control N-ERD. The treatment particularly helped reduce the severity of upper airway symptoms and alleviate the need for sinus surgery. With the administration of aspirin at 300 mg/day, there were no gastrointestinal side effects in any of the patients. In some studies, symptoms were controlled with aspirin doses higher than 300 mg.[7-16] The efficacy of 300 mg of aspirin might result from genetic differences in the study population.[17]

In N-ERD, upper and lower airway symptoms are caused by the dysregulation of arachidonic acid metabolism and increased levels of cysteinyl leukotriene by eosinophilic inflammation. The lipoxygenase pathway is over-activated due to imbalance in the lipoxygenase and cyclooxygenase (COX) pathways. COX-1 inhibition after the use of aspirin and NSAIDs causes an increase in leukotrienes that increase airway inflammation. Levels of leukotriene C4 (LTC4) synthase, LTC4, LTD4, LTE4, and 5 lipoxygenase are also increased in nasal polyp tissues of patients with N-ERD. Genetic studies have focused on cysteinyl leukotriene-related and eosinophil activating genes. *HLA* DPB1*0301 has been identified as a strong genetic marker and has been replicated in 2 ethnic groups of Poland and Korea. Patients with this allele had lower FEV1 levels and a higher prevalence of nasal polyps.[18]

We observed that long-term intake of aspirin at 300 mg/day was both effective in alleviating the need for nasal surgeries, as well as safe in patients with N-ERD. Kristen et al.[5] showed that ATAD appeared to be safe and effective with a treatment of more than 10 years, in which the mean follow-up was 15 years. Significant improvement in smell, asthma, sinus, and allergic rhinitis scores were noted. Aspirin treatment reduced the total number of sinus surgeries and improved the quality of life. Adappa et al.[16] demonstrated that the total SNOT-22 (Sino-Nasal Outcome Test) scores remained statistically unchanged from the very beginning of the post-desensitization period until the end of the 30-month follow-up period. They showed that 5 patients discontinued aspirin maintenance treatment due to gastrointestinal and respiratory side effects. Within the follow-up period, there were only 3 (9.4%) revision sinus surgeries. At lower doses such as 300 mg, high treatment efficacy and low incidence of side effects were reported.[8]

Nasal polyp is a risk factor for NSAID hypersensitivity in asthmatic patients. Kalyoncu et al.[19] compared 132 asthmatic patients with NSAID hypersensitivity and 103 asthmatic patients without NSAID hypersensitivity. There were a significantly higher number of patients with nasal polyps in the study group. Asthma was also a risk factor for NSAID hypersensitivity. Karakaya et al.[20] evaluated 1137 patients with NSAID hypersensitivity and showed that a total of 55% of patients had urticaria or angioedema, 20% had rhinitis or asthma exacerbation, and 11% had anaphylaxis after taking the NSAID. In the present study, 7 patients had a history of recurrent polyps, rhinitis, and asthma exacerbation after taking the NSAIDs before the desensitization. After the desensitization with aspirin, tolerance to other cross-reactive NSAIDs developed.[21]

Aspirin desensitization is recommended for patients with NSAID hypersensitivity who do not have asthma control with optimal medical treatment, frequently undergo ESS, and/or need to regularly take aspirin for cardiovascular diseases. Aspirin desensitization is contraindicated in patients with pregnancy, a history of severe asthma (FEV1 is less than 70% of the predicted value), gastric ulcer, and bleeding.[13] In this study, aspirin desensitization was performed in those patients who frequently underwent nasal ESS and/or whose asthma could not be controlled with optimal medical treatment.

In this study, FEV1 was followed for 12 years and there was no significant difference. However, an FEV1 decrease of approximately 35 mL/year with aging was observed in healthy people.[22] At the end of the 12-year study period, an FEV1 decrease of 400 mL was expected; however, a 178 mL decrease was observed. The study data show the possible protective effect of aspirin treatment on the lower respiratory system.

Nasal polyposis, which cannot be controlled with maximum medical treatment, is frequently observed in N-ERD. Many patients refer to ENT clinics due to recurrent nasal polyps and olfactory disorders. Surgical procedures such as polypectomy, resection of eosinophilic inflammatory tissue, and expansion of sinus ostia are performed with ESS. After the ESS, there was an improvement in lung function and quality of life of the patients, and the need for topical and systemic corticosteroids was alleviated.[23] Unfortunately, polypectomy with ESS doesn't completely treat these patients. The polyps recur, and require re-surgery in 5 years. Moreover, unstable upper airways negatively affect asthma control. The ATAD reduces nasal congestion, improves the sense of smell, prevents the regrowth of nasal polyps, alleviates the need for systemic steroids, and increases asthma control.[7] In this study, we observed that the requirement for ESS decreased significantly in 12 years after the ATAD ($P = .000$). A total of 32 ESS procedures prior to the ATAD decreased to 5 at the end of the 12 years of follow-up.

The present study had some limitations. There was a lack of a control group matched by baseline features with the intervention group. Despite the long-term follow-up, the sample size was very small. Eight patients were excluded from the study because they did not come to their regular control visits, and this caused a significant lack of data. Despite these limitations, the strength of our study is that it provides long-term follow-up data about these patients in the literature. Our study results suggest that long-term regular treatment with aspirin at a dose of 300 mg/day helps alleviate the need for nasal surgeries in patients with N-ERD. We propose that ATAD has an effect on

upper airways by reducing nasal congestion and preventing nasal polyps, and that it also possibly has effects on the lower respiratory system. However, further studies are required to provide more data on the effect of ATAD on the lower respiratory system. We believe that the present study provides additional information to the body of knowledge on this topic.

CONCLUSION

In conclusion, regular treatment with aspirin at a dose of 300 mg/day after desensitization, as a daily dose in patients with N-ERD, improves symptom scores as it alleviates the need for ESS due to nasal polyp recurrence in the long term, and is not associated with adverse effects. However, there is a need for further comparative studies to establish a definitive conclusion.

This study was presented as an oral presentation at the XXVI National Allergy and Clinical Immunology Congress between November 17, 2018 and November 21, 2018, and presented as a poster at the EAACI Digital Congress, June 6, 2020-June 8, 2020.

Ethics Committee Approval: This study was approved by the Hacettepe University Faculty of Medicine Ethics Committee (No. GO 19-206).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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