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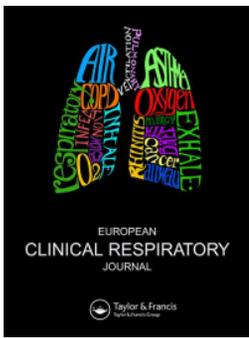
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Lung function and side effects of Aspirin desensitization: a real world study

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ABSTRACT

Introduction: NSAID-exacerbated respiratory disease (N-ERD) is mainly treated with topical and oral corticosteroids, as well as acetylsalicylic acid (ASA) treatment after desensitization (ATAD). During desensitization and ATAD, it is common to experience an exacerbation of respiratory symptoms and other side effects, which may lead to cessation of treatment.

Objectives: The aim of this retrospective follow-up study was to evaluate the effect of ATAD on lung functions and respiratory symptoms, and to clarify the occurrence of adverse events.

Methods: We analysed the patient data of 67 patients treated with ASA desensitization between 2006 and 2016 in three hospitals, concerning adverse events, respiratory symptoms, lung function tests, and reasons for discontinuation.

Results: 26 patients discontinued AD or ATAD. The most common reasons for discontinuation were lack of response (9%) and side effects (18%). ATAD did not affect lung function values in the follow-up of up to 5 years. Upper respiratory symptoms improved in 31 (52%) and lower respiratory symptoms (LRS) in 7 (10%) cases. Side effects occurred in 42 (63%) cases, the most common being dyspepsia and lower respiratory symptoms.

Conclusion: Our study suggests that ATAD has little effect on lower airway functions. Side effects were common, and discontinuation rates high.

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Asthma; rhinosinusitis; acetylsalicylic acid; aspirin; desensitization; AERD; N-ERD

Introduction

The hallmark of non-steroidal anti-inflammatory drug (NSAID) exacerbated respiratory disease (N-ERD) is a persistent eosinophilic inflammation of upper and lower airway epithelium, which is exacerbated by cyclooxygenase-1 (COX-1) inhibitor NSAIDs, including acetylsalicylic acid (ASA). N-ERD patients usually suffer from chronic rhinosinusitis with nasal polyposis (CRSwNP), asthma, and hypersensitivity to NSAIDs [1]. The sensitivity of asthmatics to COX-1-inhibitors was first described in 1902, only 3 years after the introduction of industrially manufactured ASA, aspirin [2]. The triad of CRSwNP, asthma and sensitivity to ASA was first described by Widal in 1922 and has also been known as Samter's triad and ASA exacerbated respiratory disease (AERD) [3].

The hypersensitivity to COX-1-inhibitors in N-ERD patients is not of allergic origin, but possibly due to an immunomodulatory effect on the COX pathway [4,5]. The proposed mechanism is linked to the inhibition of COX-1, which seems to lead to an imbalance in the produ-

ction of cytokines, resulting in overproduction of cysteinyl leukotriens, and underproduction of prostaglandins from their common precursor, arachidonic acid [4,5]. In N-ERD patients, COX-1-inhibitors exacerbate respiratory tract symptoms and can provoke nasal congestion, rhinitis and obstruction of the lower airways within minutes of administration. Urticaria, dyspepsia and angioedema can also occur [6].

Hypersensitivity to ASA affects 30–40% of patients with nasal polyposis and asthma [7]. Within general population, N-ERD has a prevalence of 0.3–0.9% [8]. The treatment of N-ERD patients includes topical treatments – general asthma medications and intranasal corticosteroids. Oral corticosteroids (OCS) are often needed as courses [4,9]. It has been estimated that continuous OCS treatment is needed in up to 32% of N-ERD patients [10]. CRSwNP can be resistant to medical treatment and may lead to the need of operative treatment(s) of the nasal cavities and paranasal sinuses. Clearly, a more specific treatment would be beneficial for N-ERD patients.

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In 1980, Stevenson et al. described the treatment of N-ERD with ASA desensitization (AD) and continuous ASA treatment after desensitization (ATAD) [11]. The evidence supports the use of ATAD, although there is a lack of randomized prospective studies with sufficient follow-up and number of patients [1,12–15].

ATAD is considered for N-ERD patients who have a lack of effect of medical treatment on nasal polyposis, usually having required multiple operations [16]. It has been proposed that ATAD should ideally be started after a recent polypectomy [10].

In AD phase, the dose is escalated in order to achieve ASA tolerance, which is considered generally to occur around a daily dose of 300 mg [17,18]. During AD, it is common to experience some symptoms of ASA intolerance; however, mild symptoms are not a reason for cessation. Adverse effects can occur both during AD and ATAD [4]. Side effects common to ASA, such as bruising and dyspepsia, are also frequent [10,12,19]. Leukotriene antagonist treatment can have an effect in reducing respiratory symptoms during desensitization [19].

The aim of this study was to evaluate whether AD and ATAD are safe and beneficial, with special focus on lower respiratory symptoms and lung function tests. Another aim was to gather knowledge regarding adverse events during treatment, and reasons for treatment discontinuation.

Materials and methods

This retrospective follow-up study was carried out in the Skin and Allergy Hospital and Ear-, nose- and throat (ENT) department of Helsinki University Hospital, as well as the Departments of Ear-, nose- and throat diseases in Tampere and Kuopio University Hospitals.

The study involved data of all available N-ERD patients ($n = 67$) undergoing AD consultation at these hospitals between 2006 and 2016. CRSwNP was diagnosed according to the European Position Paper on CRSwNP [20]. The patients had medical record data of endoscopic signs of nasal polyps. Asthma was diagnosed according to the criteria of the American Thoracic Society, based on lung function tests [21]. All of the patients had diagnoses of CRSwNP and asthma, as well as a history of NSAID hypersensitivity. ASA challenge tests were not done routinely in our clinics. Asthma diagnosis was verified directly from lung function values in 48 patients. In the case of 19 patients, we had no access to diagnostic lung function tests. In these cases, we considered a statement of asthma diagnosis by a clinician in medical records sufficient to confirm asthma diagnosis.

Information was collected from the hospitals' medical records in a structured form. The data collection included upper and lower airway symptoms, duration of ATAD,

ASA dosage, reasons of discontinuation of AD or ATAD, age, gender, smoking status, age of asthma onset, lung function tests (forced expiratory volume in 1 sec (FEV1) adjusted for the reference value) [22] (adjusted for height, age and ethnicity) at three data points, blood eosinophils, medications, desensitization symptoms, ASA dose in the maintenance phase, and adverse events. Also, sensitization to local aeroallergens (birch, timothy-grass, meadow fescue, mugwort, *Cladosporium herbarum*, dog, cat, horse, cow, and house dust mite) was evaluated with skin prick tests. A wheal diameter of 3 mm or larger was considered a positive reaction.

The changes in upper respiratory symptoms (URS) (rhinorrhea, nasal congestion, sense of smell) were obtained from medical records according to the information patients had given during consultation visits. The patients were grouped into categories of improved URS, no change in URS, exacerbated URS, and cessation of treatment because of URS (Table 5. Lower respiratory symptoms (shortness of breath, coughing, wheezing) were obtained in the same manner. Likewise, the patients were grouped into categories of improved lower respiratory symptoms (LRS), no change in LRS, exacerbated LRS and cessation of treatment because of LRS. Other adverse events were defined as symptoms that manifested after the beginning of AD. Lack of effect of ATAD was defined by the treating clinician based on URS.

We also investigated the available data for dose-dependent differences in the outcome of ATAD. For that reason, we divided the included patients into two groups: ASA dose of less than 300 mg, and of 300 mg or more.

The study was approved by the Ethical Committee of Helsinki and Uusimaa Hospital District (HUS/53/2016) and by the ethical committee of Hospital Districts of Helsinki and Uusimaa and Pirkanmaa (nro 31/13/03/00/2015).

The Student's *t* test, Wilcoxon signed-rank test (in pairwise comparisons), Mann Whitney U-test or chi-square test was used to evaluate the significance of results for parametric or non-parametric data accordingly. Two-tailed *P*-values of <0.05 were considered statistically significant. Statistical analysis was carried out by the SPSS 26.0 Statistical Software Package (SPSS Inc., Armonk, NY, USA).

Results

The total number of patients was 67; their mean age was 47 years (IQR 16), and 45 (65%) were female. OCS were used regularly by 9 (13%), and as short courses by 27 (40%). Four (6%) of the patients used regular antibiotic treatment because of severe airway disease to prevent exacerbations (Table 1). The median duration of ATAD was 22 months (IQR 33) with a maximum of 120 months (Table 2). At the time of the study 41 patients (61%) were still using ATAD.

Table 1. Baseline characteristics, total number of patients 67.

Characteristic		
Female (n, %)	45	67%
Age (years) (median, IQR)	47	16
FEV1 (mean, SD)	87.8%	13.3
<i>Smoking</i>		
Non-smoker	45	67%
Ex-smoker	15	22%
Current smoker	7	10%
<i>Allergy*</i>		
Prick positivity (n, %)	31	46%
Prick negativity (n, %)	19	28%
Data not available (n, %)	17	26%
Asthma onset age (years) (median, IQR)	30	20
<i>Medication</i>		
ICS (n, %)	62	93%
LABA (n, %)	47	70%
LAMA	4	6%
Regular OCS** (n, %)	9	13%
OCS as courses (n, %)	27	40%
Regular antibiotic medication	4	6%
Antihistamines	24	36%
Proton pump inhibitors	4	6%

Prick positivity was analysed against common aeroallergens, OCS: oral corticosteroids, LABA: long-acting b2-agonists, LAMA: long-acting muscarinic antagonists, FEV1: forced expiratory volume at 1 sec, ICS: inhaled corticosteroids.

Table 2. ATAD duration and dose, n = 60.

ATAD (months, median, IQR)	22	31
<i>Daily maintenance dose</i>		
Min. (mg)	50	
Max. (mg)	1500	
Mean, SD (mg)	327	242
Median, IQR (mg)	250	400
ASA dose < 300 mg (n, %)	33	55%
ASA dose ≥ 300 mg (n, %)	27	45%

ATAD: ASA treatment after desensitization, ASA: acetylsalicylic acid.

Table 3. Adverse events during AD and ATAD.

During AD	n	%
URS	7	10%
LRS	18	27%
Dyspepsia	13	19%
Urticaria	5	7%
<i>During ATAD</i>		
URS	4	7%
LRS	5	8%
Dyspepsia	5	8%
Bruises, hemorrhage	2	3%
Urticaria	2	3%
Tinnitus	1	2%

LRS: lower respiratory symptoms, URS: upper respiratory symptoms, AD: ASA desensitization, ATAD: ASA treatment after desensitization, ASA: acetylsalicylic acid.

The median maintenance dose was 250 mg (IQR 400) (Table 2).

Forty-two (63%) patients reported adverse events during AD or ATAD. Thirty-three events of adverse symptoms were linked to AD. Of these events, the most common were LRS and dyspepsia (Table 3).

The reasons for AD and ATAD discontinuation were lack of response 6 (9%), adverse events 12 (18%), and other reasons 8 (13%). AD was discontinued due to adverse events

in seven patients (10%), these being LRS [3], URS [1] and dyspepsia [4]. ATAD was discontinued due to adverse events in five patients (8%), and due to other reasons in 14 patients (23%) (Table 4). The maintenance dose was decreased (into <300 mg) in 7 patients (10%) because of adverse effects.

We found no association between the cessation of treatment and gender, skin prick test positivity, leukotriene antagonist use, or continuous OCS use ($p > 0.05$, by Fisher's

Table 4. Cessation of AD and ATAD.

	n	%
During AD	7	10%
During ATAD	19	28%
<i>Causes of cessation</i>		
URS	2	3%
LRS	3	4%
Dyspepsia	6	9%
Bruising/hemorrhage	1	2%
Non compliance	3	4%
Lack of response	6	9%
Operation/trauma/pregnancy	5	7%

LRS: lower respiratory symptoms, URS: upper respiratory symptoms, AD: ASA desensitization, ATAD: ASA treatment after desensitization, ASA: acetylsalicylic acid.

Table 5. Respiratory symptoms during ATAD.

	n	%
<i>URS</i>		
Improved	31	52%
No effect	27	45%
Exacerbated	1	1.5%
Cessation due to URS	1	1.5%
<i>LRS</i>		
Improved	6	10%
No effect	49	82%
Exacerbated	5	8%
Cessation due to LRS	0	0%

URS: upper respiratory symptoms, LRS: lower respiratory symptoms, ATAD: ASA treatment after desensitization, ASA: acetylsalicylic acid.

exact test). The mean age of the patients in whom treatment was discontinued was 43, whereas the mean age of those in ATAD was 50 ($p = 0.03$). Treatment discontinuation because of non-compliance and LRS correlated with younger age; the mean age for former being 36 ($p = 0.04$) and 32 ($p = 0.01$) for latter.

During ATAD, 31 patients (52%) reported improvement of URS, and 28 (48%) did not report any alterations in URS. Two patients (3%) reported progression of URS, and in the case of one patient, ATAD was therefore discontinued (Table 5). Concerning LRS, during ATAD 6 patients (10%) reported some improvement, and 5 (8%) reported exacerbation. There were no cases where ATAD was discontinued due to LRS.

When comparing lung function tests taken 0–12 months before AD, and during ATAD at 6–24 months and at 3–5 years data points, there was no statistically significant change in FEV1 (Table 6). We found no statistically significant association with airway symptoms and the use of continuous OCS ($p > 0.05$, by Fisher's Exact test). Concerning blood eosinophil count, the patients had a mean value of $0.47 \times 10^9/L$ prior to AD. The test was repeated 1–6 months after the onset of AD, when an increase into $0.74 \times 10^9/L$ was noted, which did not reach statistical significance ($p = 0.06$) (Table 6).

There were 33 patients (55%) receiving ASA dose of less than 300 mg and 27 patients (45%) receiving ASA

dose of 300 mg or more during ATAD. We compared these two groups for dose-dependent differences. In seven patients (10%), ASA dose was reduced in ATAD because of adverse events, these patients were included in the group receiving a dose of less than 300 mg. There was no significant difference between age or gender in these groups, neither were there significant differences with the use of continuous or intermittent OCS in the baseline (data not shown). However, the baseline FEV1 was lower in the group receiving ASA dose of 300 mg or more than in those receiving ASA dose <300 mg (83% vs 92%, $p = 0.04$).

The occurrence of URS or LRS in the patient groups with <300 mg or ≥ 300 mg ASA did not differ statistically (data not shown). There was also no significant difference in the cessation of treatment due to upper or lower respiratory symptoms, or cessation in general in the groups with <300 mg or with ≥ 300 mg ASA (data not shown). There was no significant difference in the occurrence of dyspepsia between the above-mentioned groups (data not shown).

Discussion

Our results suggest that ATAD has little or no effect on lower airway functions; FEV1 does not seem to improve or regress during ATAD. Discontinuation rates were quite

Table 6. Effect of ATAD on blood eosinophils and FEV1.

	0–12 months prior to AD	1–6 months after AD	<i>p</i> -value
B-eos (mean, SD) (n = 16)	0.47, 0.33	0.74, 0.56	0.06
	0–12 months prior to AD	6–24 months after AD	<i>p</i> -value
FEV1, SD, all (n = 45)	87.8%, 13.4	85.9%, 15.1	0.40
FEV1, SD, dose <300 mg (n = 23)	92.0%, 13.5	88.9%, 15.3	0.17
FEV1, SD, dose ≥300 mg (n = 22)	83.3%, 12.0	82.8%, 14.4	0.58

FEV1: forced expiratory volume in 1 sec, percents of predicted value, B-eos: blood eosinophils x 10E9/L, ATAD: ASA treatment after desensitization, ASA: acetylsalicylic acid.

high, and side effects were common; the most common of these being dyspepsia, URS and LRS.

With a median dose of 250 mg, 52% of the patients reported improvement of their URS. This is in line with former studies, where ATAD was estimated to be a possibly or probably effective option in N-ERD and was reported to reduce symptoms of chronic rhinosinusitis, OCS use, rate of revision surgery, and improve sense of smell and test results such as rhinomanometry [15,23]. The progression of URS and LRS symptoms was based only on medical history, obtained during consultation visits. The limitations of this approach include a lack of objective and validated measures. However, as we used very simple categories of progression of symptoms, we decided to include this aspect in our study, which focused mainly on adverse events. In our opinion, this gives a more balanced view on the progression of symptoms during ATAD.

During AD, one-fourth of our patients suffered from LRS, one-fifth from dyspepsia and one-tenth from URS. Likewise, during ATAD, LRS and dyspepsia occurred with similar frequency (8% and 8%) and 7% suffered from URS. There was no objective way to define whether respiratory symptoms were due to progression of N-ERD or due to ATAD. Altogether, one-fourth of the patients discontinued the treatment, and in the case of one-tenth, the maintenance dose was decreased because of adverse events.

In our study, the patients reported the following adverse symptoms linked to ASA sensitivity: URS, LRS, dyspepsia, bruising, haemorrhage, skin rash and tinnitus. Dyspepsia (9%) and lack of response (9%) were recognized in our study as the most common reasons for the cessation of treatment. Our findings are consistent with former studies concerning the side effects of AD [4,10,12,19].

Based on these results, we conclude that in order to achieve successful AD and ATAD, measures should be taken to prevent and reduce dyspepsia. Patients could perhaps benefit from a PPI course of longer period before and during ATAD. Also, we suggest that asthma should be in a stable state at the beginning of the treatment, especially in younger patients, who had a higher percentage of discontinuation.

We found no dose-dependent difference in the occurrence of adverse events, when comparing the groups receiving less than ASA 300 mg or more than 300 mg. However, the groups were not randomized because of the retrospective nature of our study. Instead, the ASA dose was selected according to the different customs of the clinics. For unknown reasons, the group receiving higher ATAD dose had significantly lower FEV1 already before AD.

The benefit of doses as high as 300–600 mg twice daily has been reported in former studies [1,12]. However, there has been a study showing clinical benefit from ATAD dose as low as 100 mg daily, so the question of optimal dose is yet open, and further, randomized studies are needed [17].

Currently, there are also biologic treatment options available for severe N-ERD, asthma and CRSwNP, such as anti-interleukine (IL) 5, anti-IL-5 receptor, anti-immunoglobulin E and anti-IL-4 R-alpha-receptor [24]. The long-term effects of treatment with biologics are not yet known [25]. Further studies are needed to pinpoint those who benefit from ATAD and other treatments or develop more difficult adverse reactions. Preclinical studies are also warranted to further understand the mechanism of ASA sensitivity.

Among the strengths of this study is its longitudinal setting. Also, the study consisted of a relatively high number of participants, considering the low prevalence of N-ERD, and that ATAD has been in use in Finland for only a little over a decade.

The limitations of the study include the lack of ASA challenge test on most of our patients. The diagnosis of asthma was based on the medical record information. Thus, the strict classification of N-ERD was not met in these patients. A shortcoming is also the lack of a uniform dose. We found this an interesting opportunity to compare dose-dependent side effects, even though the material was not randomized.

In this study, we concentrated mainly on side effects of ATAD. The effect of ATAD on this material, including objective measurements of upper respiratory tract, as well as the rate of operations, will be covered in another article.

According to our results, ATAD was effective for URS in half of the patients. AD and ATAD did cause adverse effects

in over half of the patients in a follow-up median of 22 months. These lead to cessation of treatment in one-fifth of the patients. The most common adverse reactions were dyspepsia and LRS. However, LRS did not lead to discontinuation of ATAD. Lung functions were stable during ATAD. Further studies are needed to understand the pathology of N-ERD and to direct ATAD to those who may benefit from it.

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Authorship statement

Sanna Toppila-Salmi and Paula Kauppi designed the study, Anu Laulajainen-Hongisto co-wrote the paper, Annina Lyly, Jura Numminen, Elina Penttilä and Johanna Sahlman collected data, Heikki Turpeinen collected data, analysed data, and co-wrote the paper.

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