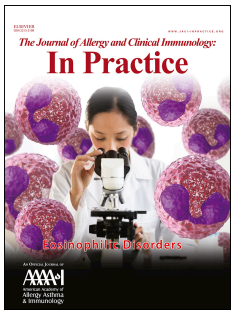

High discontinuation rates of peroral ASA treatment for CRSwNP. A real-world multi-center study of 171 N-ERD patients

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Abstract

Background: Non-steroidal anti-inflammatory drug (NSAID) exacerbated respiratory disease (N-ERD) consists of chronic rhinosinusitis with nasal polyposis (CRSwNP), asthma and NSAID intolerance. Acetylsalicylic acid (ASA) treatment after desensitization (ATAD) is a treatment option for uncontrolled N-ERD.

Objective: To evaluate peroral ATAD´s long-term effectiveness on CRSwNP disease control.

Methods: Retrospective patient record data collection (patient characteristics, sinus surgeries prior to ATAD, ATAD, follow-up data [2019]) from 171 N-ERD patients (102 ATAD patients, 69 controls with CRSwNP+N-ERD without ATAD) undergoing tertiary hospital consultation at 2001-2017. Outcome measurements were ATAD discontinuation, revision sinus surgery, corticosteroid and antibiotic courses for airway infections 2016-2019. Associations were analyzed by survival and nonparametric methods.

Results: The ATAD group had more tissue eosinophilia, symptoms and sinus surgeries prior to ATAD than others. The ATAD discontinuation rate was 63%, independent of ATAD dose or duration, usually due to side-effects. Compared to the N-ERD group without ATAD, ATAD (mean duration 2.9 years) did not affect the revision ESS rate ($p=0.21$, by log rank test) or the number of peroral corticosteroid courses/year ($p>0.05$, by Mann-Whitney U-test) during the follow-up (mean 7.6 years) despite the dose or duration of ATAD.

Conclusion: The discontinuation rate of ATAD was high (63%), and ATAD did not affect revision sinus surgery rate, nor need of peroral corticosteroids during follow-up. However, the remaining 37% of the ATAD group did continue the treatment, indicating they may have benefited from ATAD.

Highlights box:

1. What is already known about this topic? ATAD is a treatment option for uncontrolled N-ERD.

2. What does this article add to our knowledge? Yet, in our population, most patients did not benefit from ATAD and discontinued it.

3. How does this study impact current management guidelines? ATAD patients must be followed and their treatment response evaluated frequently.

Key words:

Asthma, Aspirin desensitization, Aspirin treatment after desensitization, Chronic rhinosinusitis with nasal polyposis, Non-steroidal anti-inflammatory drug-exacerbated respiratory disease

Abbreviations:

AD=Aspirin desensitization

AR=Allergic rhinitis

ASA=Acetylsalicylic acid

ATAD=Aspirin treatment after desensitization

CRS=Chronic rhinosinusitis

CRSwNP=Chronic rhinosinusitis with nasal polyposis

CT=Computed tomography

ENT=Ear, nose and throat

ESS = endoscopic sinus surgery

LM=Lund-Mackay

N-ERD=NSAID-exacerbated respiratory disease

NSAID=Non-steroidal anti-inflammatory drug

OCS=Oral corticosteroid(s)

QoL=Quality of Life

Introduction

Non-steroidal anti-inflammatory drug (NSAID) exacerbated respiratory disease (N-ERD), an inflammatory disease of the airways, usually includes a triad of chronic rhinosinusitis with nasal polyposis (CRSwNP), asthma, and hypersensitivity to acetylsalicylic acid (ASA) and other NSAIDs (1, 2). N-ERD is characterized by abnormalities of cyclooxygenase pathway, severe eosinophilic hyperplastic inflammation, and tissue remodeling with fibrosis both in paranasal sinuses and lower airways (1, 3, 4). The prevalence of N-ERD is estimated to be 9% in asthmatics. N-ERD is acquired, it is slightly more common in females and has a median age of onset around 30 years (5, 6).

Chronic rhinosinusitis (CRS) is a chronic inflammation of the nose and paranasal sinuses lasting for ≥12 weeks (7). Nasal endoscopy and computed tomography (CT) are used in CRS diagnostics (8-11). CRS affects 6-11% of the Western world´s population, causing substantial costs with a severe impact on quality of life (QoL) (12-14). CRS with and without nasal polyps are considered CRS phenotypes with different etiologies and pathomechanisms, or different degrees of inflammation (7). CRSwNP is treated with saline irrigations, nasal steroids, oral steroids, and oral antimicrobials. Surgery is considered if conservative treatment is not sufficient (2, 7). CRSwNP often leads to recurrent surgeries, especially in N-ERD patients (15, 16).

A sudden worsening of pre-existing CRS symptoms is called a CRS exacerbation (7). Although no clear definition of a CRS exacerbation exists, an escalation in CRS symptoms and management (acute symptoms of paranasal sinuses, and systemic use of antibiotics or corticosteroids) is usually considered one (17-19). CRS exacerbations are associated with poor asthma control (20). Asthma exacerbation is

121 an acute or sub-acute worsening of symptoms and lung functions, or in some cases the initial asthma
122 presentation (21).

123 Most N-ERD patients have moderate to severe asthma (2). Compared to other asthmatics, N-ERD
124 patients more often have severe asthma, and are more likely to need high dose inhaled corticosteroid
125 treatment or steroid bursts (3). Also the risk of uncontrolled asthma, asthma related healthcare visits,
126 hospitalizations, and intubations are increased in N-ERD patients (3, 5).

127 In a patient with confirmed asthma and CRSwNP, a clear history of multiple reactions with respiratory
128 symptoms within two hours after NSAID ingestion may be sufficient for N-ERD diagnosis (2).
129 However, challenge tests are used to confirm NSAID hypersensitivity in unclear cases, for research
130 purposes, or to determine the provocation dose of ASA before oral desensitization (2).
131 Contraindications for ASA challenge, ASA desensitization (AD), and ASA treatment after
132 desensitization (ATAD) include: history of anaphylactic reactions precipitated by NSAIDs,
133 uncontrolled asthma (Forced expiratory volume in one second [FEV1] <70% of the predicted value),
134 current respiratory tract infection or asthma exacerbation, renal failure, gastrointestinal bleeding,
135 pregnancy, and current treatment with β-blocker (2).

136 AD followed by ATAD is considered in N-ERD patients with insufficient response to pharmacological
137 treatment, high recurrence of nasal polyps (NP) leading to recurrent surgeries, insufficient control of
138 asthma symptoms with standard medications, need to reduce corticosteroid dose, or in patients who
139 need ASA or NSAID treatment (2, 22). Some studies suggest endoscopic sinus surgery (ESS) prior to
140 ATAD (23), or surgical removal of NPs 3-4 weeks prior to AD/ATAD (1, 2, 24-26). AD can be
141 performed as an extension of ASA challenge in outpatient settings (2, 27). According to the European
142 Academy of Allergy and Clinical Immunology (EAACI) position paper, a patient undergoing oral AD

first receives ASA 20-40 mg, the dose is gradually increased with 90-120 minute intervals on the first day in three steps to 60-100 mg, and on the second day in three steps to 325 mg (2). AD is followed by ATAD, with an effective daily ASA maintenance dose of 300-1300 mg (2, 28, 29). Intranasal ASA has also been used in ASA challenge and AD (30, 31). According to the 2020 European Position Paper on Rhinosinusitis and Nasal Polyposis (EPOS), the most commonly used AD/ATAD protocol is the Scripps clinics oral AD protocol in which, after gradual increases, a peroral dose of ASA 625mg is administered twice daily (30, 31). According to the literature, ASA could be discontinued for 48 hours without losing the desensitization (1, 25).

There is a lack of information regarding the benefits of peroral ATAD on rhinosinusitis and asthma control, and on revision ESS rates. The purpose of this retrospective, controlled, real-world multicenter study was to evaluate the effect of peroral ATAD, and its duration, on the need of revision ESS, antibiotics, and systemic corticosteroids during the follow up. We hypothesized that peroral ATAD is well tolerated and that ATAD decreases ESS rates and use of antibiotics and oral corticosteroid (OCS) courses.

Methods

Subjects

This retrospective follow-up study was carried out at the Skin and Allergy Hospital and Department of Otorhinolaryngology of Helsinki University Hospital, and at the Departments of Otorhinolaryngology of Tampere and Kuopio University Hospitals, between 2001 and 2018. Approval was obtained from the ethical committee of Hospital Districts of Helsinki and Uusimaa and Pirkanmaa (No. 31/13/03/00/2015). This study involved 171 N-ERD subjects (102 peroral ATAD patients, 69 controls

with CRSwNP+N-ERD without ATAD) undergoing surgical and/or ATAD consultation due to CRS between 2001 and 2017. Inclusion criteria were: N-ERD (e.g. a patient-record documented history of wheeze/cough/naso-ocular symptoms after ingestion of NSAID ± positive ASA challenge test result) and nasal endoscopic signs of NPs. CRSwNP was diagnosed according to the EPOS criteria (7). In Finland, N-ERD has routinely been diagnosed only by clinical examination and anamnestic information regarding NSAID intolerance. Due to the retrospective nature of this study, ASA challenge test was thus not required as a diagnostic criterion. In the control group (N=69), an additional inclusion criterion was ESS performed within one year of the consultation visit as a sign of uncontrolled CRSwNP. Exclusion criteria were unavailable or incomplete data of ATAD. All subjects were regularly monitored by otorhinolaryngologists at university hospital due to uncontrolled CRSwNP, all used maximal conservative therapy including regular intranasal steroids, and nasal lavage. Data regarding the use of OCS and antibiotic courses for CRSwNP, prior to ATAD, were included in our analysis. However, the use of additional therapies was not included in the analysis. Asthma was diagnosed according to GINA (Global Initiative for Asthma) (21), based on typical history, and lung function tests spirometry and peak expiratory flow (PEF) findings; at least 15% improvement with bronchodilator test in spirometry [in forced expiratory flow volume in one second (FEV1) or in forced vital capacity (FVC)] and/or 20% diurnal variation in PEF monitoring or 15% bronchodilator response in PEF monitoring or positive methacholine challenge test (i.e. moderate to severe bronchial hyperresponsiveness). In the ATAD group, N-ERD diagnosis was based on a positive reaction (wheeze and/or naso-ocular symptom) after intake of ASA at the hospital. In the control group, the N-ERD diagnosis was based on any positive history of wheeze/cough or naso-ocular symptoms after intake of NSAID.

The background data (age, gender, smoking, allergic rhinitis, asthma, N-ERD, history of recurrent exacerbations and use of systemic corticosteroid courses, duration of symptoms, symptoms, previous ESS, baseline endoscopic NP score, baseline LM score of sinus CT scans) were collected from patient records. Baseline ESS was defined as ESS performed within 12 months from the sinus CT scans taken during the baseline visit of sinus surgical consultation in control group, or the last ESS performed ≤ 12 months before start of ATAD in the ATAD group. Previous ESS was defined as ESS performed before the baseline visit. Follow-up ESS was defined as ESS performed after start with ATAD in the ATAD group, and in control group as ESS performed after the baseline ESS. Follow-up data were collected in 2018-2020; mean (min-max) 7.6 (0.9-16.3) years after start of ATAD, or after the consultation visit of the control group.

This follow-up data included peroral ASA-desensitization (dose, duration, side-effects, reason of possible discontinuation); revision ESS during follow-up (primary endpoint); information regarding purchased, doctor-prescribed OCS and antibiotic courses (due to CRS exacerbation and/or asthma) during 2016-2019, was obtained from the national electronic prescription system (secondary and tertiary endpoints, respectively). Discontinuation of peroral ASA desensitization as an endpoint, and the effect of peroral ASA maintenance dose and additional continuous OCS on all endpoints were also monitored.

We formed four patient groups based on ASA maintenance dose and adjuvant OCS therapy: No ATAD; ATAD with a peroral maintenance dose of <500 mg/day; ATAD with a peroral maintenance dose of ≥ 500 mg/day; ATAD with a peroral maintenance dose of ≥ 500 mg/day + adjuvant continuous OCS. The ATAD treatment was started by pulmonologists (five) or otorhinolaryngologists (two) specialized in treating N-ERD patients. Since the setting of this study is retrospective and observational, the choice of ATAD dose was made by these highly specialized and experienced

clinicians based on their clinical evaluation, and it was not affected by this study. In analyses of different endpoints, subjects with incomplete follow-up information were excluded. We also formed a variable of peroral ASA-maintenance dose*ATAD-duration (years) taking into account the total peroral ASA dose received before time of discontinuation.

Statistics

Statistical analysis was carried out by the SPSS Base 15.0 Statistical Software Package (SPSS Inc., Chicago, IL, USA). The discontinuation rate of ASA, revision ESS rate, antibiotic courses and OCS courses during the follow-up were signs of interest. Associations between ATAD dose and duration were assessed by Fisher's exact test (dichotomous), Kruskal-Wallis and Mann Whitney U tests (continuous). Differences between control and ASA-dose groups were also assessed by plotting the Kaplan-Meier survival curves and performing Log rank tests. Cox's proportional hazards models adjusted for previous ESS, baseline ESS, time (≤60, >60 days) between baseline ESS and start of ATAD, and regular OCS use during follow-up, were used to evaluate the hazard ratio (HR) of revision ESS rate between ATAD and control group, and ASA dose groups. P-values <.05 were considered statistically significant.

Results

Patient characteristics

The subject characteristics are shown in Table 1. Groups did not differ between mean age, gender, duration of symptoms, history of allergic rhinitis (AR), asthma and smoking, baseline endoscopic NP score, or total Lund-Mackay score of sinus CT scans at the time of surgical consultation (Table 1). Compared to the control group, ATAD group had higher tissue eosinophilia, higher number of previous ESS, and higher proportion of patients using OCS (Table 1).

ATAD´s discontinuation-rate

Of the ATAD group, 64 (62.7%) discontinued on average (min –max) 2.1 (0-9.3) years after ATAD start. Five patients had immediate severe adverse events (dyspnea ± skin/GI-symptoms) after ingestion of peroral ASA 35-50 mg, and did not continue ASA treatment at home (Table 1). Twenty-three (22.5%) patients reported long-term side effect(s) (tinnitus, GI pain/reflux, worsening of asthma) as reason for discontinuation, 28 (27.5%) had lack of effect; and 7 (6.9%) discontinued due to other reason(s) (such as pregnancy, operation or trauma) (Table 1). None discontinued due to no further need of ATAD because of good disease control. The peroral ASA dose was decreased to a lower, cardiological dose in six patients (500 mg -> 250 mg in two patients; 200-300 mg -> 100 mg in three patients, and 150 mg -> 75 mg in one patient) after in average one year: in four cases due to not responding to a higher ASA dose, and in one case each due to tinnitus or hemorrhage.

The maximum ASA dose mean (min-max) was 322 (50-1500) mg perorally. The ASA maintenance dose mean (min-max) 293 (50-750) mg perorally was the dose that the patient was able to use at home, and the ATAD groups were formed based on this dose. There was no statistically significant difference between the ATAD groups in ASA discontinuation-rate ($p=0.39$ by log rank test, Figure 1). When stratifying the model by the baseline ESS, the results remained similar ($p>0.05$, data not shown). In the

group of patients who were able to continue ATAD, the mean (min-max) follow-up time (= ATAD duration time) was 4.3 (0.9-1.9) years.

Revision ESS rate during the follow-up

The data of follow-up surgeries was available for 167 of 171 patients. Of all patients, the revision ESS was performed on 62 (36.3%) patients, on average (min-max) 5.5(0.5-15) years after the baseline ESS (n=141) or start of ATAD in subjects without baseline ESS (n=30). Compared to the N-ERD group without ATAD, ATAD did not affect the revision ESS rate (p=0.21, by log rank test). Moreover, there was no statistically significant difference between the ATAD dose groups in revision ESS rates during the follow up (p=0.42 by log rank test, Figure 2A). When comparing the pooled group ASA ≥ 500mg±OCS to the ASA <500mg group, or to the control group, there was no statistically significant difference in the revision ESS rate (Figures 2B-C). The mean (min-max) time between baseline ESS and start of ATAD was 100 (3-359) days. The median time between baseline ESS and start of ATAD was significantly shorter in ASA≥ 500mg+OCS group than in the other ATAD groups (Table 1). For survival models, three groups were formed: ATAD without baseline ESS, ATAD started ≤60 days after ESS, and ATAD started >60 days after ESS. The revision ESS-rate did not differ between these three groups (Figure 2D). When observing the group that started ATAD ≤60 days after ESS, there was no difference between ASA ≥ 500mg±OCS group and ASA < 500mg group in the revision ESS rate (Figure 2E).

The mean (min-max) value of ASA-maintenance dose*ATAD-duration (years) was 941 (3.3-4630) mg*years. This total dose of ASA was divided into three groups: ASA > 500 mg*years, ASA 250-500

mg*years, and ASA <250 mg*years. The revision ESS-rate did not differ between these three groups, or between controls (Figure 2F).

All patients, except those with immediate adverse events of ATAD at home, were observed in Cox´s proportional hazards models. Compared to controls, revision ESS rate was not significantly associated with ATAD maintenance dose [adjusted HR (aHR) 0.99, 95% confidence interval (CI) 998-1.001, P=0.54]. Compared to controls, revision ESS rate was not statistically significantly associated with ASA-maintenance dose*ATAD-duration mg*years (aHR 1.00, 0.999-1.000, p=0.18).

Antibiotics and peroral corticosteroid courses during the follow-up

The data of purchased OCS courses during years 2016-2020 was available for 140 patients, 58 (41%) purchased at least one OCS course/year due to N-ERD. The number of patients purchasing over ≥2 antibiotic courses/year due to N-ERD was 16/138 (12%). The proportion of patients using continuous OCS due to N-ERD was 8 (4.7%), and 3 (1.8%) due to other diseases (granulomatous polyangitis, cardiac sarcoidosis and inflammatory bowel disease) (Table 1). Five patients started a biological therapy due to N-ERD after ATAD discontinuation (Table 1).

The number of purchased antibiotic or OCS courses /year during the follow-up, did not differ significantly between the control and ATAD groups, or between the ATAD dose groups (p>0.08, Table 1). Results remained similar when excluding the patients who got immediate adverse events of ASA, and those receiving continuous OCS (p>0.1 by Kruskal-Wallis test, Figure 3). Pair-wise comparisons showed an insignificant trend that the number of purchased OCS courses /year was higher in ASA group < 500 mg, compared to the control group (p=0.073, Figure 3A). The number of purchased OCS courses /year was higher in the group who had received ASA 250-500 mg*year compared to the

295 control group or the group who had received ASA ≥ 500 mg*year (p=0.007, p=0.018 respectively,
296 Figure 3B).

297

298 ***Responder analysis***

299 The ATAD patients were analyzed in two groups based on their treatment response and ability to
300 continue ATAD. Discontinuing patients were defined as those who discontinued ASA due to lack of
301 effect or due to side effect. Responders were defined as being able to continue ATAD and not needing
302 revision ESS during follow-up. The total follow-up time was longer in the discontinued group
303 (p=0.021, Table 2). The other baseline or follow-up data did not differ between responders and non-
304 responders/discontinuing patients (Table 2).

305

306 **Discussion**

307

308 The discontinuation-rate of ATAD was very high (63%) in this retrospective, real-world, multicenter
309 study performed in the Finnish population. While 37% of the patients continued ATAD, we did not see
310 clear dose-response effects of ATAD in respect to revision ESS or purchased antibiotic or OCS courses
311 during the follow-up.

312 As in the literature (1, 2), also our study patients with N-ERD usually had a triad of CRSwNP, asthma
313 and hypersensitivity to NSAIDs. ATAD is considered in uncontrolled N-ERD patients with difficult to
314 treat symptoms and insufficient response to other pharmacological or surgical treatments (2, 22). Our
315 study findings were in line with this; the ATAD group was more symptomatic, had higher tissue
316 eosinophilia and more prior ESS, compared with the control group consisting of patients with severe
317 CRSwNP and N-ERD not undergoing ATAD. The groups were otherwise very similar, especially in
318 regard to LM score and endoscopic NP score, making study comparisons reliable. Since AD was
319 performed in the ATAD group, their diagnosis of N-ERD can be considered confirmed also by ASA
320 challenge, whereas NSAID intolerance diagnosis in the control group was based on anamnestic
321 information.

322 Most studies concerning AD and ATAD and their benefits are, like ours, retrospective. The existing
323 prospective, randomized, placebo controlled ATAD studies suggest that ATAD has a beneficial effect
324 on symptoms, and rhinosinusitis and asthma control (32, 33). Ibrahim et al. (2014) reported in a
325 retrospective study of 111 patients, that 73% of those in ASA maintenance therapy, had general
326 improvement in their symptoms (32). They reported improvement in symptoms, QoL, reduced need for
327 rescue therapy for both upper and lower airway symptoms, and improvement in sense of smell or taste

(32). In their double-blind, placebo controlled study comparing results of ATAD in asthmatics with (n=20) or without (n=14) ASA intolerance, Swierczynska-Krepa et al. (2014) report a beneficial effect on the rhinosinusitis and asthma control of those with ASA intolerance (33). Esmaeilzadeh et al. (2015) reported clinical efficacy of ATAD (ASA 650mg twice daily for 1 month, followed by 325mg twice daily) in improving symptoms, need for medication, QoL, sinus opacification and lung functions in their randomized, double-blind, placebo controlled study of 34 patients with N-ERD (34). Mortazavi et al. (2017) reported improvements in QoL, symptoms, and FEV1 values in their randomized, double-blind clinical study including 38 patients (35). In our study, 37% of the patients continued ATAD, probably benefitting from it. Our study was, however, not able to verify this benefit because symptom scores were not used. It is thus also possible that this is only a placebo effect. This clearly warrants further studies, it would be interesting to find ways to identify the subgroup of patients benefiting from ATAD, possibly using biomarkers.

In our study, ASA doses were lower compared to those usually mentioned in the literature (2, 28-31, 34). However, Fruth et al. (2013) have reported beneficial effects of ASA 100mg daily in patients with N-ERD (36). It seems that our population does not tolerate high doses of ASA. The reason for this is unknown, and could include e.g. genetic factors, clearly warranting further studies. Our results show that compared to controls, ATAD did not affect the need of OCS or antibiotic courses during follow-up, we also did not see clear dose-response effects of ATAD in respect to these.

Previous studies have shown that the following factors associate with the frequent revision ESS: male gender, young adult age, smoking, occupational exposure, radiological inflammatory findings in frontal sinus(es), presence of NPs, asthma, and N-ERD (37). Also tissue eosinophilia is associated with polyp recurrence (38).

CRSwNP often leads to recurrent surgeries, and ASA intolerance is associated with a higher prevalence of uncontrolled CRS after operative treatment (15, 16, 39). Early surgical intervention of CRS may be associated with less sinusitis-related postoperative health care utilization (40). Also the timing of ATAD in relation to ESS has been discussed, and part of the literature suggests ESS prior to ATAD (1, 2, 23-26). Due to the retrospective nature of this study, the timing of ESS in relation to ATAD was not constant. Our results show that compared to controls, ATAD did not affect revision ESS rates, nor did we see dose-response effects of ATAD in respect to this. In our study, there were no statistically significant differences in the revision ESS rates between the controls and different ATAD groups based on ASA dose and time between baseline ESS and ATAD. The group taking ASA ≥ 500mg±OCS did not have a statistically significantly lower risk for revision ESS in the follow-up. Peroral corticosteroids should usually not be used with ATAD, since it is known that peroral corticosteroid treatment combined with ASA increases the risk of gastrointestinal bleeding, necessitating careful patient selection, additional proton pump inhibitor treatment and monitoring for gastrointestinal side effects (2, 41).

A recent study from the USA reported good long term benefits of ATAD, in this study only 12% had discontinued the treatment (42). We had a much higher discontinuation rate (63%) of ATAD. Treatment responses may vary in different populations, this warrants future studies. Whenever possible, attempts were made to keep the patients on ATAD by treating side effects and lowering ASA doses. The most common reason for ATAD discontinuation in our study was side effects, lack of effect was less common. ATAD discontinuation did not depend on dose or duration.

The optimal ATAD dose, duration or indication has not been validated in randomized, placebo-controlled studies. The diagnostics or medical and surgical treatment of N-ERD were not standardized in our retrospective cohort. Due to real-world effectiveness study and the nature of this cohort the

patient groups were non-randomized. As also in other real-world ATAD studies, despite including all ATAD patients treated at our study hospitals, the number of patients is relatively small. The even smaller number of patients in the subgroups makes statistical analyses between them challenging, this may have affected our results. We acknowledge that, due to the retrospective study setting, the unfortunate lack of disease-specific QoL measurements, symptom scores, and lack of information regarding the sense of smell limit the interpretation of the findings. There might also have been limitations in the variables collected from patient records.

This study provides new data regarding the real-world use of ATAD in three tertiary centers. Our findings point out the need for standardizing N-ERD diagnostics and treatment by international, multicenter, prospective controlled setups.

The discontinuation-rate of ATAD was very high (63%) in this retrospective, real-world, multicenter study. We did not see dose-response effects of ATAD in respect to revision ESS or purchased antibiotic or OCS courses during the follow-up. However, 37% of the ATAD group did choose to continue the ATAD treatment, probably benefitting from it at least to some extent.

Author contributions

AL-H performed data collection and writing of this article. ST-S planned this study, collected & analyzed data and wrote this article. HT, SV, JN, JS, PK, PV, and MH participated in data collection. All authors critically reviewed the final article text.

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515 Figure legends:

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517 **Figure 1.** Predictive effect of ASA (Acetylsalicylic acid) desensitization (ATAD) dose to discontinuation. Data of
518 NSAID-exacerbated respiratory disease patients undergoing surgical and ASA desensitization consultation
519 (2001-2017), able to start ATAD, were used with follow-up data of endoscopic sinus surgery (ESS). Those (5)
520 with immediate adverse events were excluded from analysis. Comparisons between ASA; OCS = oral
521 corticosteroid(s). P-values by log rank test.

522 **Figure 2.** Predictive effect of ATAD (ASA desensitization [AD] followed by ASA treatment after AD) to the time
523 until revision endoscopic sinus surgery (ESS) and/or nasal polypectomy was performed according to the Kaplan-
524 Meier method. Data of CRSwNP patients undergoing CRS-surgical consultation in 2001-17 were used with
525 follow-up data of ESS.

526 **Figure 3.** Number of purchased prescribed oral corticosteroids (OCS)/year (for CRSwNP and/or asthma). Data
527 analyzed from N-ERD patients undergoing surgical consultation due to CRS 2001-2017 with follow-up data of
528 prescribed medication from electronic database 2016-2020. ASA= Acetylsalicylic acid. Data excluded from
529 analysis for 5 patients with immediate adverse events and 11 receiving OCS. P-values by Mann Whitney U test.
530 Only p-values <0.1 are shown.

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536 **Table 1.** Patient background and follow-up characteristics.

	No ATAD	ATAD				
		ATAD <500mg/day	ATAD ≥500mg/day	ATAD ≥500mg/day+ OCS	p^1	p^2
	n=69	n=67	n=27	n=8		
Female gender, n (%)	40 (58.0)	44 (65.7)	15 (55.6)	5 (62.5)	.74	.63
Age, median (Q1-Q3)	47.0 (31.4-58.8)	46.9 (37.9-55.8)	45.5 (39.5-52.5)	48.3 (41.0-53.5)	1.0	.90
Current smokers, n (%)						
No	52 (80.0)	56 (84.8)	22 (95.7)	7 (87.5)	.35	.27
Current	13 (20.0)	10 (15.2)	1 (4.3)	1 (12.5)		
AR, n (%)						
No	31 (44.9)	26 (39.4)	11 (40.7)	4 (50.0)	.88	.64
Yes	38(55.1)	40 (60.6)	16(59.3)	4 (50.0)		
Asthma, n (%)						
No	3 (4.3)	1 (1.5)	1 (3.8)	0 (0.0)	.67	.40
Yes	66 (95.7)	66 (98.5)	25 (96.2)	8 (100.0)		
Duration of symptoms (y), median (Q1-Q3)	10 (4-23)	13 (8-25)	12.5 (8.5-15.75)	27.5 (15-39)	.069	.19
A history of ≥ 1 OCS course /y						
No	35 (54.7)	30 (46.2)	9 (34.6)	2 (25.0)	.21	0.11
Yes	29 (45.3)	35 (53.8)	17 (65.4)	6 (75.0)		
A history of ≥ 4 antibiotic course /y						
No	30 (58.8)	34 (55.7)	19 (70.4)	6 (75.0)	.52	0.86
Yes	21 (41.2)	27 (44.3)	8 (29.6)	2 (25.0)		
NP eosinophilia						
< 30%	15 (37.5)	5 (14.7)	0 (0)	0 (0)	.065	0.19
≥ 30%	25 (62.5)	29 (85.3)	4 (100)	1 (100)		
Endoscopic NP score, median (Q1-Q3)	5 (4-6)	5 (4-6)	4.5 (3.5-6)	4 (3.5-6)	.58	.29
Total LM score of sinus CT scans, median (Q1-Q3	16 (14-22.5)	20 (15-22)	19.5 (14-21)	15.5 (13.25-18.5)	.36	.52

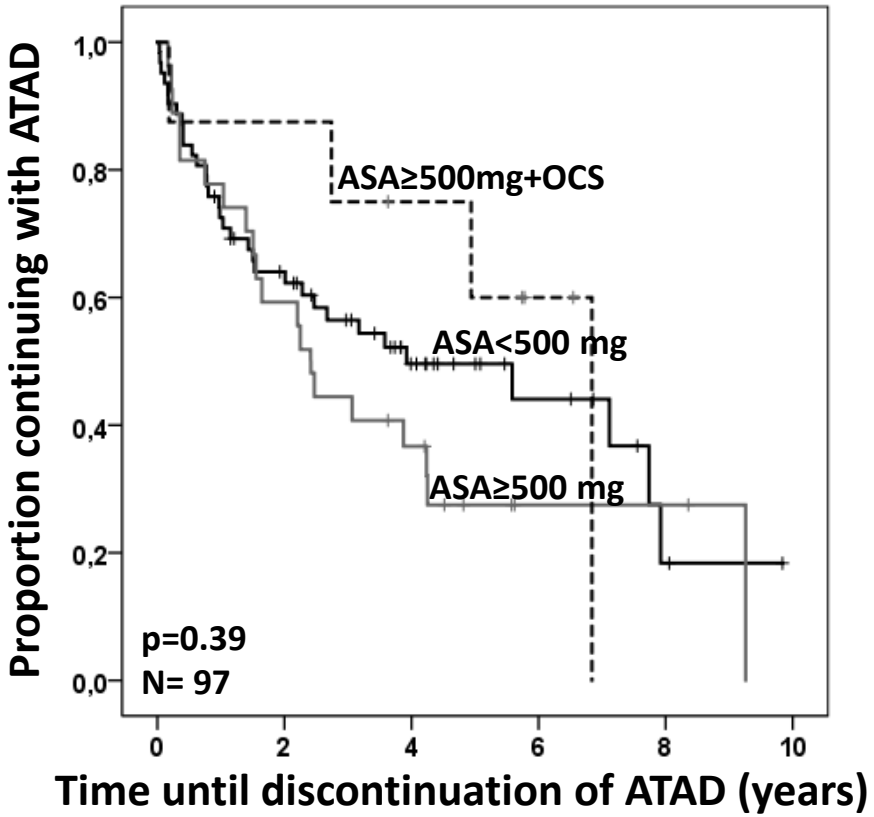
Number of previous ESS, median (Q1-Q3)	1 (0-2)	2 (2-5)	2 (1-4)	3.5 (2-5)	**<.001**	**<.001**
Baseline CRS-surgery in 1 year after the first visit (before ATAD)					**<.001**	**<.001**
No surgery	0 (0)	20 (32.8)	4 (16.0)	1 (12.5)		
Polypectomy ±ESS without opening of ethmoidal cells	26 (37.7)	20 (32.8)	6 (24.0)	3 (37.5)		
Polypectomy ±ESS with partial opening of ethmoidal cells	29 (42.0)	16 (26.2)	6 (24.0)	1 (12.5)		
Polypectomy ±ESS with total opening of ethmoidal cells	14 (20.3)	5 (8.2)	9 (36.0)	3 (37.5)		
Time between baseline ESS and start of ATAD, median (Q1-Q3)		137 (51-250)	45 (19-100)	25 (18-48)	**<.001**	-
Duration of ATAD (y), median (Q1-Q3)	-	2.2 (0.6-4.2)	2.4 (1.0-4.2)	5.3 (3.0-6.4)	.10	-
Reason for discontinuation of ATAD						
Total adverse events, n (%)	-	40 (60.6)	20 (74.1)	4 (50.0)	.37	-
Immediate adverse event[3]		5 (23.9)	11 (40.7)	1 (12.5)		
Long-term side effects[4]		16 (7.5)	0 (0)	0 (0)		
No effect/disease relapse		16 (23.9)	4 (14.8)	3 (37.5)		
Other[5]		4 (6.0)	3 (11.1)	0 (0)		
Nr of antibiotic courses /year during 2016-19, median (Q1-Q3)	0.5 (0-1.3)	0.5 (0-2)	0.3 (0-1.1)	0.5 (0-1)	.56	.86
Nr of OCS courses /year during 2016-19, median (Q1-Q3)	0 (0-1)	0.5 (0-1)	0.5 (0.5-1.3)	0 (0-0.5)	.084	.11
Nr of patients using continuous OCS, n (%)						
Due to any reason	1 (1.4)	2 (3)	0 (0)	8 (100)	**<.001**	**.029**
Due to N-ERD	0 (0)	0 (0)	0 (0)	8 (100)	**<.001**	**.022**
Due to other disease[6]	1 (1.4)	2 (3)	0 (0)	0(0)	.80	1.00
Start with biological therapy (after ATAD discontinuation)	0 (0)	1 (1.5)	1 (1.5)	3 (37.5)	**<.001**	.082
Revision ESS in 5 years, n (%)						
No	34 (58.6)	34 (59.6)	13 (68.4)	6 (85.7)	.54	.60
Yes	24 (41.4)	23 (40.4)	6 (31.6)	1(14.3)		

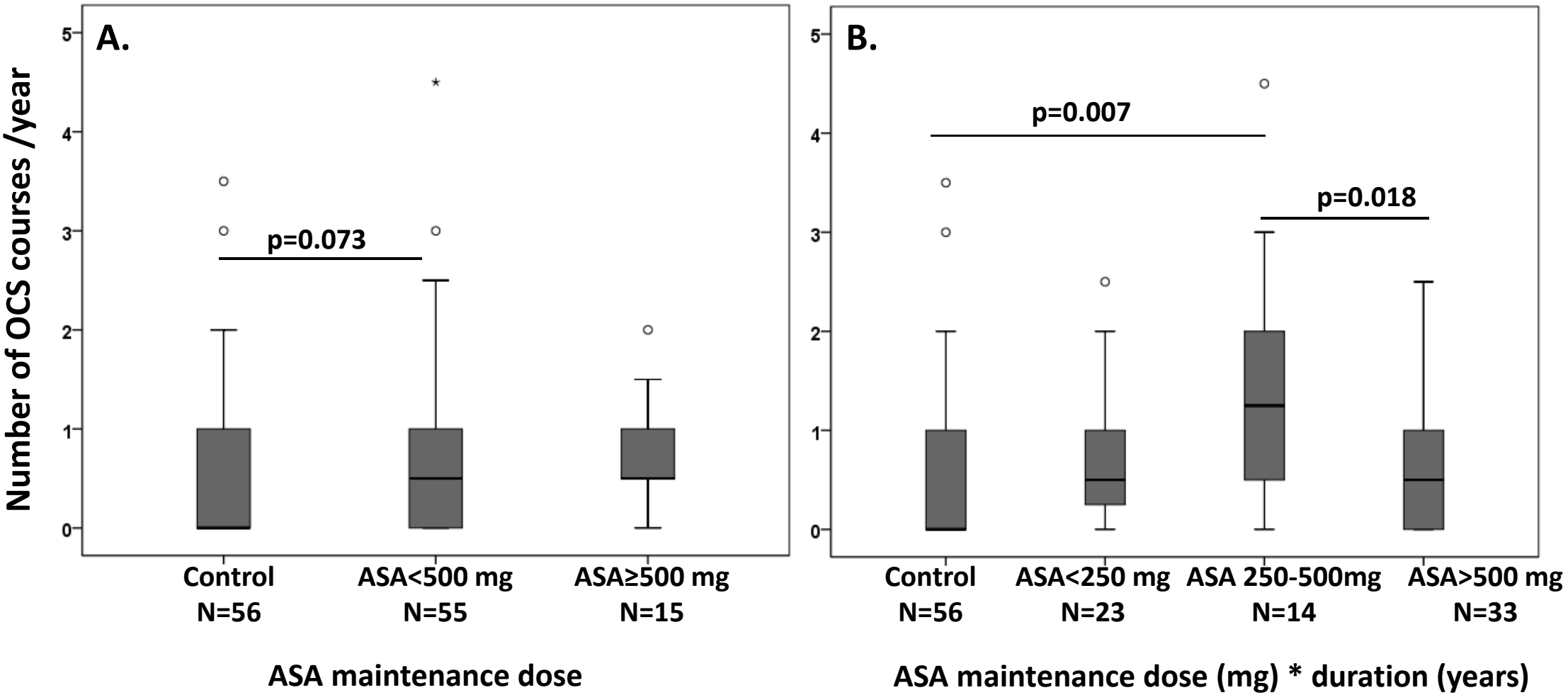
AD= aspirin desensitization, ATAD= AD followed by ASA treatment after desensitization, AR= allergic rhinitis, ASA=aspirin, CRS= chronic rhinosinusitis, ESS= endoscopic sinus surgery, N-ERD = patient-reported NSAID-exacerbated respiratory disease, NP=nasal polyps, OCS= oral corticosteroid(s). P values by Fisher´s exact test (dichotomous variables) or Kruskal Wallis and Mann Whitney U test (continuous variables). Q1= 25% percentile, Q3= 75% percentile. Bold text indicates a statistically significant difference with a P value less than 0.05. [1]p-value by comparing all 4 groups. [2]p-valua by comparing no ATAD and ATAD groups, [3]Severe acute dyspnea ±skin/gastrointestinal (GI) symptoms. [4]tinnitus, GI pain/reflux, worsening of asthma. [5]Operation, trauma, pregnancy/lactation. [6]granulomatous polyangitis, cardiac sarcoidosis and inflammatory bowel disease.

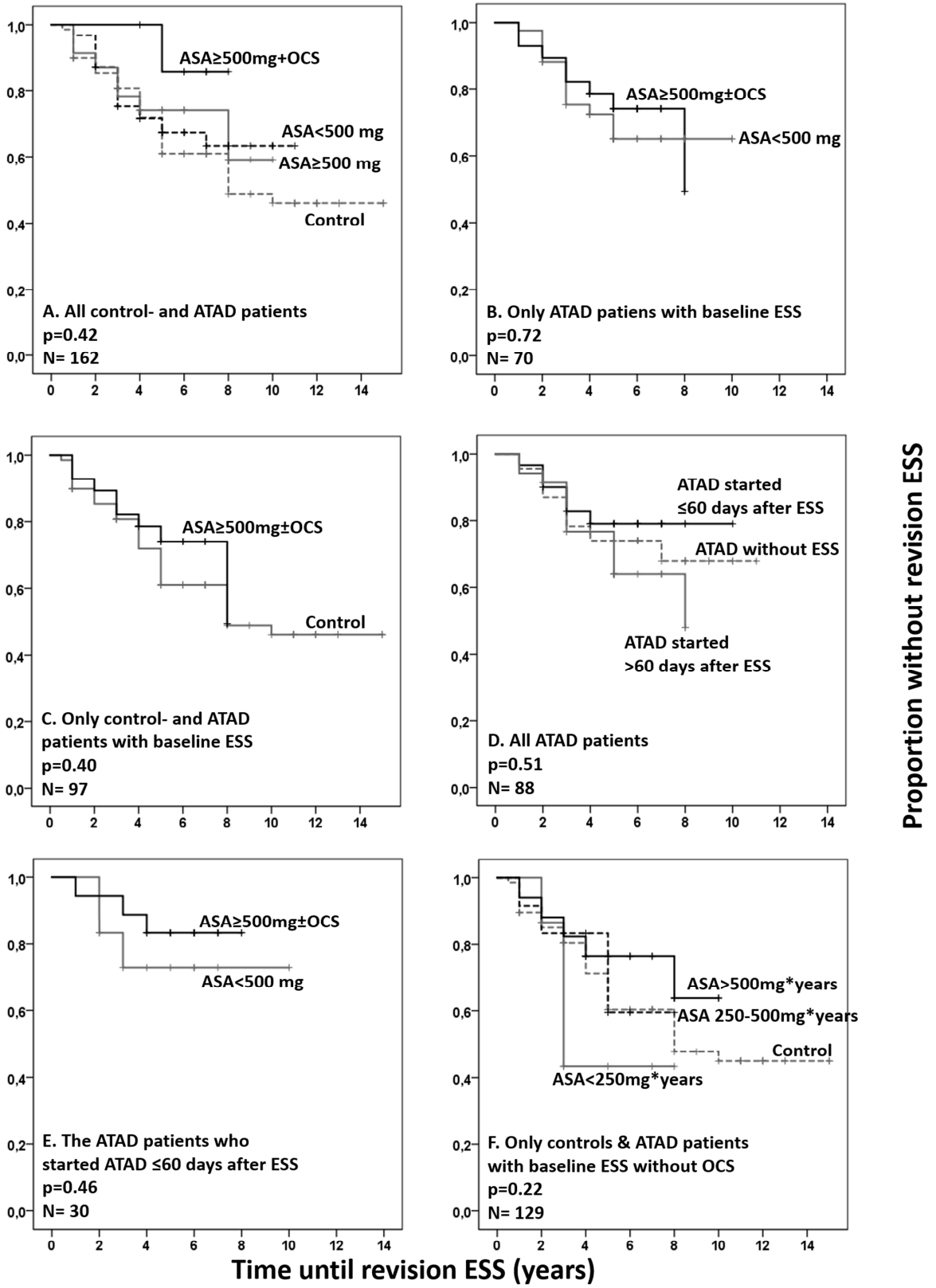
544 **Table 2.** Comparison of baseline and follow up data of ATAD patients. ATAD patients were divided into two
545 groups: those who discontinued ASA, and those who continued ASA and were not re-operated during the
546 follow-up (=responders).

	ATAD discontinued N=57	ATAD continues & no revision ESS N=36	p
Female gender, n (%)	37 (64.9)	23 (63.9)	1.0
Age, median (Q1-Q3)	44.6 (37.4-55.5)	46.4 (39.8-54.9)	.66
Current smoker, n (%)	7 (12.7)	4 (11.1)	1.0
AR, n (%)	33 (58.9)	20 (55.6)	.83
Asthma, n (%)	55 (98.2)	35 (97.2)	1.0
Duration of symptoms (y), median (Q1-Q3)	13 (8-20)	11 (3-30)	.20
≥ 1 OCS course /y	35 (64.8)	17 (47.2)	.13
≥ 4 antibiotic course /y	20 (37.7)	14 (41.2)	.82
NP eosinophilia ≥ 30%	19 (95.0)	12 (75.0)	.15
Baseline endoscopic NP score ≥ 4, n (y)	37 (78.7)	27 (81.8)	.78
Baseline total LM score ≥ 16, n (y)	41 (75.9)	20 (60.6)	.15
≥ 3 previous CRS-surgeries, n (%)	28 (49.1)	17 (47.2)	1.0
Baseline polypectomy± ESS before start of ATAD	36 (63.2)	30 (83.3)	.059
Baseline total ethmoidectomy before start of ATAD	7 (12.3)	9 (25.7)	.16
Time between baseline ESS and start of ATAD ≤ 60 days	16 (50.0)	14 (48.3)	1.0
Maximum dose of ASA mg/day, median (Q1-Q3)	250 (100-500)	250 (100-500)	.46
Maintenance dose of ASA mg/day, median (Q1-Q3)	250 (100-500)	250 (100-500)	.21
Duration of ATAD (y), median (Q1-Q3)	1.0 (0.3-2.6)	4.3 (3.6-5.6)	**<.001**
Total Follow-up time (y), median (Q1-Q3)	6.3 (4.6-8.0)	4.8 (4.0-6.3)	**.021**
> 2 antibiotic courses /year during 2016-19, n (%)	6 (12.8)	2 (6.9)	.70
> 1 OCS course /year during 2016-19, n (%)	11 (23.4)	7 (22.6)	1.0
Continuous OCS during the follow-up	3 (5.3)	6 (16.7)	.084
Start with biological therapy (after ATAD discontinuation)	4 (7.0)	1 (2.8)	.65
Revision ESS in 5 years, n (%)	25 (50.0)	0 (0)	**<.001**

AD=aspirin desensitization, AR=allergic rhinitis, ASA=aspirin, ATAD=AD followed by ASA treatment after desensitization, CRS=chronic rhinosinusitis, ESS=endoscopic sinus surgery, NP=nasal polyps; OCS= oral corticosteroid(s). P values by Fisher´s exact test (dichotomous variables) or Kruskal Wallis and Mann Whitney U test (continuous variables). Q1= 25% percentile, Q3= 75% percentile. Bold text indicates a statistically significant difference with a p value less than 0.05. None of the ATAD patients discontinued ATAD due to good response. Only patients with available follow-up data were included. Those who continued ASA but were re-operated (n=6) were excluded.


Proportion continuing with ATAD
1,0
0,8
0,6
0,4
0,2
0,0
ASA≥500mg+OCS
ASA<500 mg
ASA≥500 mg
p=0.39
N= 97
0
2
4
6
8
10
Time until discontinuation of ATAD (years)




ASA≥500mg+OCS
ASA<500 mg
ASA≥500 mg
Control
A. All control- and ATAD patients
p=0.42
N= 162
ASA≥500mg±OCS
ASA<500 mg
B. Only ATAD patiens with baseline ESS
p=0.72
N= 70
ASA≥500mg±OCS
Control
C. Only control- and ATAD patients with baseline ESS
p=0.40
N= 97
ATAD started ≤60 days after ESS
ATAD without ESS
ATAD started >60 days after ESS
D. All ATAD patients
p=0.51
N= 88
ASA≥500mg±OCS
ASA<500 mg
E. The ATAD patients who started ATAD ≤60 days after ESS
p=0.46
N= 30
ASA>500mg*years
ASA 250-500mg*years
Control
ASA<250mg*years
F. Only controls & ATAD patients with baseline ESS without OCS
p=0.22
N= 129
Proportion without revision ESS
Time until revision ESS (years)