

Aspirin Desensitization: Useful Treatment for Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) in Aspirin-Exacerbated Respiratory Disease (AERD)?

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Abstract Aspirin intolerance syndrome is due to disturbances in the arachidonic acid metabolism implicating both the lipoxygenase and cyclooxygenase pathways. This results in imbalances of eicosanoid, leukotriene and prostaglandin synthesis. Thus, preinflammatory cysteinyl leukotrienes increase and antiinflammatory prostaglandins (PG) such as PGE₂ decrease. Clinically, intolerance reactions to nonsteroidal antiinflammatory drugs (NSAIDs) can lead to different clinical manifestations; five phenotypes of the aspirin intolerance syndrome are listed in the ENDA classification. Aspirin-exacerbated respiratory disease (AERD) is the most common phenotype characterized by an eosinophil-dominated inflammatory disease of the airways that presents clinically with nasal polyps, chronic sinusitis and bronchial asthma. About 34 % of patients with aspirin-induced asthma and rhinosinusitis are thought to have AERD. Important biochemical findings in many AERD patients are increased basal leukotriene levels (at least in cell cultures) that excessively increase after intake of COX-1 inhibitors. Aspirin desensitization uses the repetitive application of aspirin to induce a tolerance to NSAIDs, especially COX-1 inhibitors. After a dose-increase phase reaching a threshold dose, a dose-continuation phase is performed. For application, the nasal, bronchial, oral and intravenous routes have been described.

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Aspirin desensitization has been proven to be efficacious and safe and was able to reduce the need for other medications in AERD patients.

Keywords Samter triad · AERD · Chronic rhinosinusitis · CRSwNP · Nasal polyps · Aspirin intolerance · Adaptive deactivation · Aspirin desensitization · Treatment

Introduction

Aspirin-exacerbated respiratory disease (AERD) is an eosinophil-dominated inflammatory disease of the airways that is often clinically characterized by nasal polyps, chronic rhinosinusitis and bronchial asthma. The complex of intolerance to nonsteroidal antiinflammatory drugs (NSAIDs), nasal polyps and bronchial asthma is called Samter's triad or Samter's disease (Morbus Samter) or Widal's disease (Morbus Widal) in the European literature [1]. Pathophysiologically, AERD is a non-allergic inflammation of the upper and lower airways with chronic courses that may lead to acute exacerbations upon the intake of COX1-inhibitors [2, 3].

While reactions to aspirin (acetyl salicylic acid: ASA) were reported only shortly after its development by Hirschberg in 1899 [4], in 1922 Widal et al. were the first to portray the association of aspirin sensitivity, aspirin-induced asthma (AIA) and nasal polyposis [5]. The full clinical picture was subsequently pointed out in studies by Samter and Beers [6] showing that symptoms of chronic sinusitis and nasal polyps often occur early in the disease.

Pathophysiology of AERD

The underlying pathophysiological mechanisms of the ASA intolerance syndrome seem to be disturbances in the

arachidonic acid metabolism implicating both the lipoxygenase and cyclooxygenase pathways, while no IgE-dependent mechanisms have been found in AERD [7, 8]. This may result in an imbalance of eicosanoid, leukotriene and prostaglandin synthesis. Thus, cysteinyl leukotrienes such as leukotriene A⁴, B⁴, C⁴, D⁴ and E⁴ increase and antiinflammatory prostaglandins (PG) such as PGE₂ decrease [8, 9].

Important biochemical findings in many AERD patients are increased basal leukotriene levels (at least in cell cultures) that excessively increase after intake of COX-1 inhibitors [10].

This increase in leukotrienes (LTs) is based on a pharmacological competitive inhibition of the COX-1 enzymes leading inter alia to a reduced synthesis of prostaglandin E₂ (PGE₂). Since PGE₂ is among the most important inhibitors of 5-lipoxygenase and thereby of leukotriene synthesis, this synthesis will proceed unchecked leading to an excessive production of the leukotrienes LTB₄, LTC₄, LTD₄ und LTE₄ [11].

The reduced production of the broncho- and vasodilator mediators PGI₂ and PGE₂ leads to a clinically evident imbalance of leukotriene-induced broncho- and vasoconstriction and thereby to the typical clinical intolerance reaction [12]. Moreover, the reduced PGE₂ synthesis results in a destabilization of mast cells, which liberates the preformed mediators histamine and PGD₂ and produces leukotrienes leading to generalized symptoms [13, 14].

The outstanding pathophysiological relevance of the reduced PGE₂ production is supported by the fact that PGE₂ prevents both the clinical intolerance reaction and the increase of LTE₂ in urine after inhalation of aspirin [15•]. However, why AERD patients have elevated basal levels of leukotrienes and why COX-1 inhibition leads to this dramatic imbalance of the arachidonic acid metabolism with excessive leukotriene levels in patients with AERD, but not in healthy subjects, are not conclusively explained by the mechanism outlined and still not fully understood today [7, 12, 16]. An increased expression of LTC₄ synthetase was found in AERD patients as well as an increased expression of cysLT₁ receptors at effector cells [17, 18]. These findings of imbalance in the arachidonic acid pathway were helpful in explaining high leukotriene levels and chronic inflammatory changes in the airways of patients with AERD [7, 10, 16]. Studies investigating the molecular mechanisms of metabolic imbalances using molecular genetic expression techniques and molecular biology methods were undertaken to identify relevant biomarkers for the detection of AERD [14, 19•].

Reduced activity of the cyclooxygenases COX-1 and COX-2 leads to an imbalance of the lipoxygenase metabolism followed by a shift from prostaglandin/prostacyclin production toward leukotrienes (LTs). A reduced prostaglandin-E₂-(PGE₂) level leads to instable mast cell membranes with

liberation of histamine followed by increased vascular permeability and edema. COX-1 and COX-2 downregulation can be found in nasal polyps from both aspirin-tolerant [20, 21] and -intolerant [22–24] patients. This topic has been reviewed in detail by Guilemany et al. [25] and Mullol et al. [26•].

Regarding the pathomechanism of the eicosanoid imbalance in AERD, it is known that nasal polyps have a reduced expression of COX2-mRNA and thus less PGE₂ compared to polyp tissue of ASA-tolerant patients [11, 27]. Liu et al. [27] were able to demonstrate in a mouse model that a missing microsomal PGE₂-synthase-1 and reduced induction of PGE₂ synthesis induce an AERD-like eosinophilic pulmonary inflammation with eosinophil-dominated bronchovascular cell infiltrates and following bronchoconstriction and mast cell activation. A provocation with lysine-aspirin leads to a continuously increased airway resistance in combination with an activation of lung mast cells and increased cysteinyl leukotriene (CYS-LT) production [27]. Cys-LTs include LTC₄, LTD₄ and LTE₄ and are metabolized from arachidonic acid via the 5-lipoxygenase pathway. They mediate bronchoconstriction, eosinophil chemotaxis and activation, collagen deposition, airway hyperresponsiveness and vascular permeability [28]. The application of a PGE₂ analog or a selective E-prostanoid 2 receptor agonist before the lys-aspirin provocation blocked the response by 90 %. The increase in airway resistance and mast cell products was inhibited by leukotriene (cys-LT₁) or 5-lipoxygenase antagonists (montelukast or zileuton).

This may open new horizons for the development of new AERD drugs, e.g. toward prostanoid receptors or thrombocytes or thromboxane-selective antagonists.

Steinke et al. [29] examined the exact composition of the inflammatory milieu in AERD including the influence of INF-γ on the maturation, differentiation and functionality of eosinophils. They detected type T_{H1} and T_{H2} lymphocytes and the cellular source of cytokines in polyp tissue of patients with AERD and aspirin-tolerant CRSwNP. AERD patients, in contrast to ASA-tolerant patients, were characterized by a pronounced expression of IFN-γ that was found to be released by eosinophils.

Roca-Ferrer [11] isolated fibroblasts from five AERD patients and five healthy volunteers and incubated them over 72 h with IL-1β (10 ng/ml), which is known to induce COX-2. Prostaglandin E₂ (PGE₂) concentrations and expression of COX-1 and COX-2 were measured, and increased PGE₂ and COX-1 expression was found in the healthy volunteers but not in the AERD group. Moreover, IL-1β induced a significant increase of COX-2 expression in the healthy volunteers and a much lower increase in the AERD patients.

Prevalence of ASA Intolerance

Aspirin intolerance is thought to be underestimated: in a population of 500 patients with AIA studied in the European Network of Aspirin-Induced Asthma (AIANE), 18 % were unaware of aspirin intolerance before having aspirin challenge tests [30]. More interestingly, when patients with AIA also suffered from concomitant rhinosinusitis, even 34 % were unaware of their disease before testing [31, 32]. Other data reveal incidence rates from 0.6 % to 2.5 % and in adult asthmatics even from 4.3 % to 11 % [31].

Aspirin Desensitization

In 1976, Zeiss and Lockey described the paradoxical finding that ASA-intolerant patients revealed a 3-day refractory period after oral aspirin challenge [33]. This report marked a new therapeutic option in the management of aspirin-sensitive patients. Since then, aspirin desensitization has used the repetitive application of ASA to induce a tolerance towards NSAID, especially COX-1 inhibitors [30, 34–38]. After a dose-increase phase reaching an individual threshold dose, a dose-continuation phase is performed, usually with orally applied aspirin [31, 35]. In larger patient groups, aspirin desensitization was proven to be efficacious and safe and was able to reduce the need for other medications in AERD patients [34, 39].

Mechanisms of Aspirin Desensitization

ASA intolerance is characterized by tissue infiltration by mast cells and eosinophils, overexpression of cysteinyl leukotrienes along with upregulation of cysteinyl leukotriene-1 receptors [40]. COX-1-inhibiting NSAIDs result in a reduction of prostaglandins (especially PGE₂) and an increase in cysteinyl leukotriene production. Aspirin desensitization is clinically effective in carefully selected patients; however, its mechanism of action remains poorly understood [40].

Burnett et al. reviewed the current understanding of how aspirin desensitization works on an immunological basis [28]. According to this hypothesis, aspirin desensitization may inhibit the IL-4 activated STAT6 pathway. Thus, the IL-4/STAT6-mediated production of cysteinyl-leukotrienes (especially LTE₄) and expression of the cys-LT₁ receptor are reduced, followed by decreased airway inflammation and clinical improvements. Moreover, induction of PGE₂ and of COX-1 and COX-2 enzymatic activity may be part of the mechanism [40]. Other molecular mechanisms and effects on tyrosine kinases as well as on other cytokines and cell types are still not understood [28].

Aktas et al. [41] examined the cytokine-expression (IL-2, IL-4, IFN- γ) of CD4⁺ T-lymphocytes in AERD patients with asthma before and 1 month after a 4-day desensitization therapy. AERD patients ($n=12$) were included and compared with 15 healthy volunteers and 12 ASA-tolerant asthmatics who took aspirin as well. IFN- γ -secreting CD4⁺ T-lymphocytes were reduced in AERD before desensitization ($p=0.04$) compared to the control group but did not change with desensitization (15.6 ± 4.4 before vs. 15.1 ± 5.9 % after). The levels of IL-2, IL-4 and the subsets of lymphocytes were not different before and after desensitization and did not differ from the control groups.

Contraindications

So far, contraindications to aspirin desensitization are not well defined, but should be discussed as much as allergen immunotherapy with special considerations for aspirin's side effects [40]. We therefore recommend the following as contraindications (Table 1):

- Pregnancy
- Acute infections
- Partly or uncontrolled bronchial asthma $\geq$ grade III (moderate to severe persistent): FEV₁ <70 % of the norm, PEF (“peak expiratory flow”) $\leq$ 80 %
- Local or systemic intake of β -blockers
- Intake of Marcumar® (phenprocoumon = warfarin or of other coumarin derivatives)
- Severe cardiovascular, liver and kidney diseases
- Gastritis, gastroesophageal reflux, gastroduodenal ulcerations
- Mastocytosis
- Non-compliant patient
- High risk for injuries due to professional or personal lifestyle considerations

All contraindications must be regarded as relative, and an individual evaluation should be performed in each patient individually.

Application Routes

Based on these findings, various desensitization protocols and routes of administration have been elaborated in the last 3 decades using the bronchial, endonasal, oral and intravenous routes.

1) Oral application

At present, the per oral application of aspirin can be regarded as the standard treatment approach to aspirin

Table 1 Indications and contraindications for aspirin desensitization (modified from [40, 69–72])

Indications	History of aspirin intolerance Positive provocation test with aspirin
Contraindications	Pregnancy β-Blocker Autoimmune diseases Unstable asthma Cardiac diseases Gastric ulcers Bleeding disorders Anticoagulation therapy Children (relative) Patients with sinus surgery 3 months prior to aspirin desensitization

desensitization [34]. It has been used since Stevenson et al. first described two cases of AIA patients experiencing a desensitization with incremental doses of oral aspirin followed by daily oral continuation therapy [37]. Improvements of aspirin-sensitive asthma as well as a reduction of CRSwNP were seen in both patients. A randomized DBPC crossover study using oral aspirin desensitization in 25 patients with CRSwNP and aspirin-sensitive asthma was published by the same group shortly thereafter using a daily dose of 325 to 1,300 mg aspirin over a 3-month period [42]. A significantly better improvement of nasal symptoms as well as a reduced need for nasal corticosteroids was seen in the verum group compared to the placebo group; however, this effect was much smaller with regard to bronchial symptoms: only half of the patients experienced an improvement in their asthma symptoms.

A total of 107 patients with CRSwNP and AIA were then retrospectively evaluated [35]. From these, 65 patients underwent aspirin desensitization while the control group ($n=42$ patients) avoided all NSAIDs. Patients receiving aspirin desensitization had a significantly better outcome with regard to the number of hospitalizations and emergency room visits, upper airway tract infections, olfactory measures and paranasal sinus surgery. Side effects were seen in about 20 % of the 65 desensitized patients, being mainly gastric complaints.

A long-term study over 6 years using aspirin desensitization with a daily peroral dose of 1,300 mg found a significant reduction in polyp growth and recurrence rate of nasal polyps in AERD patients [34] with a decline in the need for operations from one per 3 years to one per 9 years. However, the number of emergency room visits and need for inhaled corticosteroids remained unchanged in this study.

In a similar study on 172 patients, a reduction in the incidence of purulent sinusitis was shown, declining from

an average of five times per year before therapy to less than half of that after therapy [39]. Interestingly, a clinical response rate of 67 % was evident as early as 6 months following the beginning of the treatment indicating a relatively early therapeutic effect of the desensitization therapy. Furthermore, these results persisted for 1 to 5 years. A discontinuation rate of 9 % was seen with the long-term therapy due to gastric symptoms; this was lower compared to the data of the same group from 1996 [34]. The authors related these findings to the use of misoprostol and proton pump inhibitors, both of which became available in recent years.

2) Nasal application

Nasal aspirin desensitization has mainly been used in cases of predominating nasal symptoms. Patriarca et al. applied increasing doses of lysine-aspirin corresponding to 20, 200 and 2,000 µg of aspirin nasally until a maximum weekly dose of 2,000 µg was reached in 43 patients suffering from CRSwNP [43]. In a 5-year follow-up, recurrence rates of nasal polyps were significantly lower in the aspirin-treated group compared to the control group. Moreover, a first randomized DBPC crossover trial of topical nasal aspirin desensitization using a low-dose (16 mg) protocol has been reported in 11 AERD patients with CRSwNP [44], but clinical efficacy was only poor in this nasal desensitization study.

3) Bronchial application

This route of administration has been developed on the premise that refractory tolerance could be achieved by repeated bronchial inhalation with lysine-aspirin [36]. Due to possible severe side effects, it has not been widely used so far.

4) Intravenous application

Pfaar and Klimek were the first to use the intravenous route for ASA desensitization [45]. Patients ($n=36$) with a positive history of ASA intolerance, (recurrent) sinonasal polyps and a positive test result on the functional eicosanoid test (FET) were treated with increasing doses of lysine-aspirin up to 900 mg intravenously per day [40]. Systemic adverse reactions were seen in 27 patients equaling 6.6 % of all therapeutic doses. Of all systemic reactions, 81 % were first-degree reactions, while 19 % were second-degree reactions (according to the EAACI grading system). Third- or fourth-degree systemic reactions have not been revealed.

This study indicated that the intravenous route for the initial increasing phase of ASA desensitization might be a safe procedure comparable to oral application without severe complications. However, in contrast to oral application, the intravenous procedure might have the advantage of allowing interruption of ASA application by stopping the infusion in case of (beginning) systemic reactions [40]. Undoubtedly, more studies are necessary to

Table 2 Outcome of aspirin desensitization treatment in AERD patients aspirin-related side effects

Reference	Kind of study/evel of evidence	Number (n) of patients	Inclusion criteria	Maintenance ASA dose (mg)	Groups	Follow-up	Main results/outcome
Stevenson et al, 1984 [73]	RCT / Level I	25	AERD, CRSwNP positive oral ASA provocation test	Individual, 325–1,300 mg	ASA-D duration: 3 months	3 months	Improvement of nasal symptoms and reduction of nasal corticosteroids. Lower respiratory tract symptoms were not significantly changed during treatment. Nevertheless, half of the patients experienced improvement of their asthma symptoms
Sweet et al. 1990 [35]	RCS/level III	107	AERD, positive oral ASA provocation test	Individual: range 325–2,600 mg Previous Mean dose: 1,300 mg daily discontinued (n=30)	ASA-D (n=35) vs. non-D (n=42) vs ASA-D (mean 2 years)	ASA-D: mean 46 months Non-D: mean 102 months Previous ASA-D: 32 months	Significantly improved clinical outcome (compared to baseline) in the ASA-D group, but return to baseline after ASA treatment in the “previous ASA-D” group. Predominant reason for stopping the ASA-treatment in the previous ASA-D group: gastric side effects (n=12)
Stevenson et al. 1996 [34]	RCS/level III	78	AERD, CRSwNP positive oral ASA provocation test	Individual, mean 1,214 mg	ASA-D duration: 1–3 years (n=29) 3–6 years (n=36)	1 – 6 years. Mean: 3.1 years. Evaluable: 65 patients	Improved outcome in both groups for acute sinusitis and hospitalizations ($p<0.0001$), clinical parameters and steroid medication ($p<0.05$) Reduction in the frequency of sinus surgery for NP Gastrointestinal side effects in 9 patients (dropout)
Berges-Gimeno et al. 2003 [39]	RCS/level III	172	AERD, CRSwNP positive oral ASA provocation test	Individual, mean 1,138 mg	ASA-D duration: ≥ 1 year (n=126)	1 – 6 years	Improved outcome ($p<0.0001$) for: no. of acute sinusitis, smell scores, nasal and asthma scores after 6 months 67 % of the patients responded to the treatment. After the 126 patients who fulfilled 1 year treatment 87 % responded. Discontinuation because of side effects in 24 patients
Havel et al. 2013 [59]	RCS/level III	89	AERD, CRSwNP grade 2, inclusion following surgery	500 mg, daily	ASA-D (n=56) vs. non-D (n=33) min.	18 months,	For the ASA-D group: Less NP ($p<0.000$) Improved VAS rating for asthma ($p=0.25$) and sinonasal ($p=0.11$) conditions. Improved QoL for sinonasal and general items
Comert et al. 2013 [74]	CS/level IV	40	AERD, CRSwNP grade 2, inclusion following surgery	300 mg, daily	ASA-D, no control group	3 years (n=18)	For 3 years ASA-D group:
Rozsasi et al. 2008 [54]	PCS/level II	14	AERD, CRSwNP positive oral ASA provocation test	100 vs. 300, daily	ASA-D 100 mg, vs. ASA-D 300 mg	1 year (n=29)	Fewer systemic corticosteroids per year ($p=0.001$) Fewer sinusitis episodes per year ($p=0.03$) Less revision sinus surgery per year ($p=0.002$) Side effects: gastric (n=2), ecchymosis (n=1) After 1 year recurrence of NP in 100 % (100 mg group) vs. 0 % (300 mg group).

Table 2 (continued)

Reference	Kind of study/level of evidence	Number (n) of patients	Inclusion criteria	Maintenance ASA dose (mg)	Groups	Follow-up	Main results/outcome
Gosepath et al. 2001 [75]	CS/level IV	39	AERD, CRSwNP positive <i>in vitro</i> test	300 mg, daily	ASA-D, no control group	mean: 27 months	No NP recurrence Side effects: gastric (n=2)
	CS/level IV	30		100 mg daily	ASA-D group only, no control group	1 year,	Normalization of <i>in vitro</i> test levels in 83 % of the patients. Marked improvement (endoscopy) of NP in 12 patients, no recurrence in 14 patients, steady state in 3 patients and NP progression in 1 patient
Fruth et al. 2013 [60]	RCT/level I	70	AERD, CRSwNP positive <i>in vitro</i> test Inclusion following sinus surgery	100 mg daily.	ASA-D vs. non-D (control)	3 years Evaluable: 31 patients. ASA-D (n=18), controls (n=13)	Improved outcome in the ASA-D group for: NP relapse (p=0.07), QoL (p=0.03) and clinical complaints (p<0.01) High dropout rate not due to aspirin-related side effects

ASA-D=aspirin desensitization group, non-D=control group, no aspirin desensitization
 CS=case series, PCS=prospective comparative study, RCS=retrospective cohort study,
 NP=nasal polypsis

investigate further safety and efficacy parameters of intravenous application in comparison to other administration routes [40]. In most cases, NSAIDs are much better tolerated after aspirin deactivation [46].

Mühlmeier et al. [47] were able to demonstrate that, using the intravenous route for ASA provocation, more than 50 % of their 61 AERD patients showed a first response at the peak at threshold doses between 16–400 mg of lysine-aspirin with a median of 157±104 mg. This may explain why aspirin desensitization with continuation doses of 300 mg, as often used currently, improves nasal symptoms better than other organ symptoms, since 92 % of their AERD responders had a threshold level below 300 mg aspirin.

Dosage/Application Time

Up to now, no clear dose-effect studies have been published for aspirin desensitization. Therefore, no international recommendations exist with regard to up-dosing in the initiation phase or the daily continuation dose [45, 48]. A daily continuation dose of 1,300 mg was applied by Stevenson et al. in early studies [34]. Lee and Stevenson used a dose of 1,300 mg over 4 weeks with a reduction to 650 mg daily in the continuation phase [49]. Since then, several other dosing schedules have been described [50] [51] [52], with an overview in [40]. Today, most authors recommend daily continuation doses of 300 mg aspirin [40, 50–52], which can be increased to a daily dose of 500 mg aspirin [50], while others [53] recommend continuation doses of only 100 mg daily. Rozsasi et al. performed a rare study comparing continuation doses of 100 mg vs. 300 mg aspirin in AERD patients with CRSwNP [54]. The group receiving a continuation dose of 100 mg aspirin revealed 100 % nasal polyp recurrence, whereas the control group receiving 300 mg aspirin per day had no recurrent polyps after a median follow-up of 27 months [54]. In the future, further prospective, controlled, dose-response studies need to be performed with regard to efficacy as well as safety measures of aspirin desensitization [52].

Concomitant Medication in Aspirin Desensitization

In a study by White and Stevenson, a medication with the leukotriene antagonist montelukast reduced bronchial but not nasal symptoms during aspirin desensitization [43]. Oral and topical glucocorticosteroids as well as bronchodilators should be continued as usual. Antihistamines and nasal decongestants should be discontinued 48 h before the beginning of a desensitization to avoid a possible masking of adverse events [43].

Aspirin Desensitization and Paranasal Sinus Surgery

Massive growth of polyps in the nasal and paranasal sinuses is removed by endonasal surgery using endoscopic or microscopic techniques [55]. However, the recurrence rate is quite high: in a prospective study of 227 patients operated on for nasal polyposis between 1993 and 2001, a significantly higher rate of recurrences was revealed in the AIA group compared to patients tolerant to ASA [56]. Also Jantii-Alanco et al. determined the recurrence rate of nasal polyps after endonasal sinus surgery to be almost three times higher in AERD than in ASA-tolerant patients with CRSwNP and bronchial asthma [57]. However, Jang et al. found no differences in disease-specific quality-of-life outcomes (SNOT-20) in CRSwNP patients with and without AERD 3 years after paranasal sinus surgery [58], while the Lund-Kennedy nasal endoscopy scores were significantly more severe in AERD vs. control groups. Aspirin desensitization was able to reduce the necessity for surgical interventions in recurrent nasal polyps in 65 AERD patients from one surgery per 3 years to one surgery per 9 years [34].

In another study by Havel et al. [59], 65 patients with AERD with asthma were treated after sinus surgery with a daily dose of 500 mg oral aspirin in comparison to a control group of 81 patients receiving a topical nasal corticosteroid (mometasone). After 18 months, the desensitization group was significantly better compared to the control group with regard to nasal symptoms such as obstruction, anterior and posterior rhinorrhea, olfaction, facial pain and sleep quality. However, no differences were seen in bronchial symptoms.

Fruth et al. [60] performed a randomized DBPC study in 70 patients with AERD who received a continuation dose of 100 mg daily. Primary endpoint of this study was polyp recurrence after 36 months. According to the high dropout rate, only $n=31$ patients could be evaluated at the end of the study period ($n=18$ patients from the verum group, $n=13$ patients from the placebo group). In 8 of these 31 patients, a reoperation was necessary during the study period ($n=6$ from the placebo group; $n=2$ from the verum group). Polyp recurrences were significantly less in the verum group ($p=0.07$) and the nasal polyp score significantly lower ($p=0.07$) after 36 months of treatment. Quality of life was better in the verum group ($p=0.0324$) as were clinical symptoms ($p<0.05$), and no aspirin-related adverse events were seen. In contrast, in a study by Rozsasi et al., all AERD patients ($n=7$) with CRSwNP showed recurrent nasal polyps under a continuation dose of 100 mg aspirin, whereas a control group receiving 300 mg aspirin per day had no recurrent nasal polyps [54].

Starting Time Point for Aspirin Desensitization

Aspirin desensitization in AERD often requires a combination with (revision) sinus surgery. Beginning desensitization at a

time point 4 weeks after the operation has been recommended [40]. According to our own experience, the best period to start aspirin desensitization is 6 to 12 weeks after sinus surgery.

Conclusions

Based on the current clinical and pathophysiological data, desensitization to aspirin can be regarded as an effective treatment in AERD. Significant clinical improvement of quality of life, olfactory function, nasal polyposis and asthma has been described and well documented for AERD patients (Table 2). Especially for improving nasal symptoms and reducing recurrence of nasal polyposis, aspirin desensitization followed by daily aspirin doses of (a minimum of) 300 mg seems very effective. Hereby, the frequency of surgical interventions in recurrent nasal polyps was shown to decrease from one surgery per 3 years to one surgery per 9 years.

Although these clinical improvements are well documented in the literature, several factors and aspects of aspirin desensitization are still a matter of debate. First, concerning the diagnostic procedures, further studies on the predictive value of clinical provocation testing are needed in order to adjust the optimal starting point for desensitization. In addition, studies to evaluate and compare alternative routes of aspirin delivery (e.g., oral vs. intravenous) may help to assess safety aspects of the initial desensitization protocol as well as the effect and safety issues of different maintenance doses and treatment durations. Accordingly, treatment optimization will be the major goal of future studies on aspirin desensitization to establish validated protocols to treat nasal polyposis in AERD patients as effectively and safely as possible.

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Compliance with Ethics Guidelines

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- Of major importance

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